Postpartum haemorrhage: prevention

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ABSTRACT

INTRODUCTION: Loss of more than 500 mL of blood is usually caused by failure of the uterus to contract fully after delivery of the placenta, and occurs in over 10% of deliveries, with a 1% mortality rate worldwide. Other causes of postpartum haemorrhage include retained placental tissue, lacerations to the genital tract, and coagulation disorders. Uterine atony is more likely in women who have had a general anaesthetic or oxytocin, an overdistended uterus, a prolonged or precipitous labour, or who are of high parity. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of drug and of non-drug interventions to prevent primary postpartum haemorrhage? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2007 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 29 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: active management of the third stage of labour, carboprost injection, controlled cord traction, ergot compounds (ergometrine/methylergotamine), immediate breastfeeding, misoprostol (oral, rectal, sublingual, or vaginal), oxytocin plus ergometrine combinations, oxytocin, prostaglandin E2 compounds, and uterine massage.

QUESTIONS

INTERVENTIONS

Key points

- Loss of more than 500 mL of blood is usually caused by failure of the uterus to contract fully after delivery of the placenta, and occurs in over 10% of deliveries with a 1% mortality rate worldwide.

  Other causes of postpartum haemorrhage include retained placental tissue, lacerations to the genital tract and coagulation disorders.

  Uterine atony is more likely in women who have had a general anaesthetic or oxytocin, an over-distended uterus, a prolonged or precipitous labour, or who are of high parity.

- Active management of the third stage of labour, with controlled cord traction, early cord clamping plus drainage and prophylactic oxytocic agents, reduces the risk of postpartum haemorrhage and its complications.

  Active management increases nausea, vomiting, and headache, but generally improves maternal satisfaction.

  Controlled cord traction may reduce the risk of retained placenta and need for medical treatment, and can be used in any resource setting.

  Uterine massage is often used to prevent postpartum haemorrhage, and is supported by a single RCT. It can be used in any resource setting.

- Oxytocin has been shown to effectively reduce the risk of postpartum haemorrhage compared with placebo.

  A combination of oxytocin plus ergometrine may be slightly more effective than oxytocin alone, although there are more adverse effects.

- Ergot alkaloids seem as effective as oxytocin, but are also associated with adverse effects including nausea, placenta retention, and hypertension.

- Prostaglandin treatments vary in their efficacy, but are all associated with adverse effects.

  Carboprost and prostaglandin E2 compounds may be as effective as oxytocin and ergot compounds, but have gastrointestinal adverse effects, such as diarrhoea.

  Misoprostol seems ineffective compared with placebo when administered orally, rectally, or vaginally, and is associated with adverse effects including shivering and fever.

  Sublingually administered misoprostol may be more effective than placebo in preventing postpartum heamorrhage (evidenced by a single RCT). Sublingual misoprostol has similar effects to injected agents, but is associated with more adverse effects. Confirmatory data would be helpful, as these results differ substantially from the many RCTs on other modes of administration of misoprostol, and it is unclear if there is something unique about sublingual administration.

  When available, oxytocin, ergometrine, or combinations are preferred to misoprostol, as misoprostol seems less effective, and is associated with more adverse effects. Sublingual administration is the preferred route for misoprostol.

DEFINITION

Postpartum haemorrhage is characterised by an estimated blood loss greater than 500 mL. The leading cause of postpartum haemorrhage is uterine atony — the failure of the uterus to contract fully after delivery of the placenta. Postpartum haemorrhage is divided into immediate (primary) and delayed (secondary). Primary postpartum haemorrhage occurs within the first 24 hours after delivery, whereas secondary postpartum haemorrhage occurs between 24 hours and 6 weeks after delivery. This review addresses the effects of strategies for prevention of postpartum haemorrhage after vaginal delivery in low- and high-risk women, specifically looking at strategies to prevent uterine atony. Future updates will examine strategies to prevent postpartum haemorrhage due to other causes, as well as treatment strategies.

INCIDENCE/ PREVALENCE

The WHO reports that obstetric haemorrhage causes 127,000 deaths annually worldwide, and is the world's leading cause of maternal mortality. Nearly all of these deaths are due to postpartum haemorrhages, which occur nearly 14 million times each year. [1] In Africa, haemorrhage is estimated to be responsible for 30% of all maternal deaths. [2] The imbalance between resource-rich and resource-poor areas probably stems from a combination of: increased prevalence of risk factors such as grand multiparity, lack of safe blood banking, no routine use of prophylaxis against haemorrhage, and lack of measures for drug and surgical management of atony.

AETIOLOGY/ RISK FACTORS

In addition to uterine atony, immediate postpartum haemorrhage is frequently caused by: retained placental tissue; trauma such as laceration of the perineum, vagina, or cervix; rupture of the uterus; or coagulopathy. Risk factors for uterine atony include: use of general anaesthetics; an over-distended uterus, particularly from multiple gestations, a large fetus, or polyhydramnios; prolonged labour; precipitous labour; use of oxytocin for labour induction or augmentation; high parity; chorioamnionitis; or history of atony in a previous pregnancy.

PROGNOSIS

Most postpartum haemorrhage, particularly in Europe and the USA, is well tolerated by women. However, in low-resource settings, where women may already be significantly anaemic during pregnancy, blood loss of 500 mL is significant. Although pregnancy-related death is rare in the USA, postpartum haemorrhage accounts for 17% of deaths. [3] Maternal death is 50–100 times more frequent in resource-poor countries, and postpartum haemorrhage is responsible for a similar proportion of deaths as in the USA. Other significant morbidities associated with postpartum haemorrhage include renal failure, respiratory failure, multiple organ failure, need for transfusion, need for surgery including dilatation and curettage, and, rarely, hysterectomy. Some women with large blood loss will later develop Sheehan's syndrome.

AIMS OF INTERVENTION

To prevent death; to reduce volume of blood loss, need for manual removal of placenta, need for transfusion, and need for medical or surgical treatment of postpartum haemorrhage.

OUTCOMES

Primary outcomes include maternal mortality, serious maternal morbidity including need for admission to an intensive care unit, renal failure, respiratory failure, multiple organ failure, need for additional medical (e.g. drugs like oxytocin, blood transfusions) or surgical (e.g. hysterectomy, hypogastric artery ligation, uterine curettage) treatment. Secondary outcomes include the mother's ability to care for the newborn, ability to breastfeed, patient satisfaction, volume of blood loss (estimated

by drop in haemoglobin or haematocrit, or measured by direct collection). Adverse effects of postpartum haemorrhage include retained placental tissue, anaemia, Sheehan's syndrome, and uterine inversion.

METHODS

Clinical Evidence search and appraisal September 2007. The following databases were used to identify studies for this review: Medline 1966 to September 2007, Embase 1980 to September 2007, and The Cochrane Database of Systematic Reviews 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for all databases, Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved were assessed independently by two information specialists using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language (including "open" studies) and containing at least 40 people of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. The only ergot compound that we searched for was ergometrine/methergine (ergonovine, methylergonovine, ergotrate, methylergometrine, ergotamine). In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency, which are continually added to the review as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 36). To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs.

QUESTION **What are the effects of non-drug interventions to prevent primary postpartum haemorrhage?**

OPTION **ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOUR**

Morbidity

Compared with expectant management or with expectant management plus routine oxytocin Active management of the third stage of labour, consisting of controlled cord traction, early cord clamping plus drainage, and a prophylactic oxytocic agent is more effective at reducing postpartum haemorrhage of 500 mL or of at least 1000 mL. Active management is also more effective at reducing related morbidities including mean blood loss, postpartum haemoglobin less than 9 g/dL, blood transfusion, or the need for supplemental iron postpartum (high-quality evidence).

Need for further interventions

Compared with expectant management or expectant management plus routine oxytocin Active management of the third stage of labour, consisting of controlled cord traction, early cord clamping plus drainage, and a prophylactic oxytocic agent, is no more effective at reducing the need for manual or surgical removal of the placenta (high-quality evidence).

Adverse effects

Compared with expectant management alone or in combination with oxytocin Active management is more likely to increase adverse effects such as nausea and vomiting (high-quality evidence). However, active management reduces the length of the third stage of labour, and women are less likely to be dissatisfied when their third stage of labour is actively managed.

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits:

We found one systematic review (search date 2000), which identified five RCTs including 6477 women in maternity units in the UK (4 RCTs) and in the United Arab Emirates (1 RCT). Three were in low-risk populations, and risk status was not specified in the other two. [4] All women in the active-management group received controlled cord traction, early cord clamping plus drainage, and a prophylactic oxytocic agent (see comment below). Four RCTs compared active management versus expectant management, whereas one RCT used intravenous oxytocin alone after placental delivery as control intervention. All but one RCT limited entry to women with singleton vertex deliveries. The review found that, compared with expectant management or oxytocin alone, active management significantly reduced rates of postpartum haemorrhage (4 RCTs, 6284 women: 163/3126 [5%] with active management *v* 428/3158 [14%] with expectant management; RR 0.38, 95% CI 0.32 to 0.46), severe postpartum haemorrhage (defined as clinically estimated blood loss at least 1000 mL, 4 RCTs, 6284 women: 27/3126 [1%] with active management *v* 83/3158 [3%] with expectant management; RR 0.33, 95% CI 0.21 to 0.51), postpartum haemoglobin level less than 9 g/dL (4 RCTs, 4255 women: 52/2108 [3%] with active management *v* 132/2147 [6%] with expectant management; RR 0.40, 95% CI 0.29 to 0.55), need for transfusion (5 RCTs, 6477 women: 25/3229 [1%] with active management *v* 75/3248 [2%] with expectant management; RR 0.34, 95% CI 0.22 to 0.53), and for additional medication (5 RCTs, 6477 women: 112/3229 [4%] with active management *v* 555/3248 [17%] with expectant management; RR 0.20, 95% CI 0.17 to 0.25). The review found no significant difference between active management and expectant management or oxytocin in the

need for surgical evacuation of retained placental tissue (3 RCTs, 4636 women: 22/2299 [1%] with active management *v* 30/2337 [1%] with expectant management; RR 0.74, 95% CI 0.43 to 1.28), and secondary postpartum haemorrhage (2 RCTs, 3124 women: 20/1551 [1%] with active management *v* 23/1573 [2%] with expectant management; RR 0.88, 95% CI 0.49 to 1.60). A subgroup analysis excluding high-risk women (1 RCT) yielded similar results. The review found no significant difference in the need for manual placenta removal overall (5 RCTs, 6477 women: 54/3229 [2%] with active management *v* 45/3248 [1%] with expectant management; RR 1.21, 95% CI 0.82 to 1.78), with four RCTs finding no significant difference between interventions, but one RCT (using intravenous ergotamine as the oxytocic agent) finding the need for manual placenta removal to be much higher with active management, thus skewing the pooled estimate compared with the control intervention. Despite the increased risk of adverse effects (see harms below), a significantly smaller proportion of women reported dissatisfaction with their third stage management when it was actively managed (1 RCT, 1466 women: 27/748 [4%] with active management *v* 46/718 [6%] with expectant management; RR 0.56, 95% CI 0.35 to 0.90).

Harms: The systematic review found that, in general, compared with expectant management or oxytocin alone, active management of the third stage of labour significantly increased adverse effects (vomiting: 3 RCTs, 3407 women: 159/1680 [10%] with active management *v* 74/1727 [4%] with expectant management, RR 2.19, 95% CI 1.68 to 2.86; nausea: 3 RCTs, 3407 women: 247/1680 [15%] with active management *v* 139/1727 [8%] with expectant management, RR 1.83, 95% CI 1.51 to 2.23; headache: 3 RCTs, 3407 women: 24/1678 [1%] with active management *v* 13/1727 [0.8%] with expectant management, RR 1.97, 95% CI 1.01 to 3.82). [4] One RCT found a higher proportion of women with "bleeding needing readmission or antibiotics" with active compared with expectant management; the confidence interval was wide and compatible with a large increase or a moderate reduction (1429 women: 5/705 [0.7%] women with active management *v* 0/724 [0%] women with expectant management; RR 11.30, 95% CI 0.63 to 203.92). Another RCT found no significant difference between interventions in maternal fatigue at 6 weeks (1 RCT, 1557 women: 105/745 [14%] with active management *v* 113/752 [15%] with expectant management; RR 0.95, 95% CI 0.74 to 1.22).

Comment: The RCTs used a range of oxytocic agents as part of active management, with oxytocin alone given in one RCT, ergometrine in one RCT, and a fixed combination of oxytocin plus ergometrine in the other three. [4]

OPTION CONTROLLED CORD TRACTION

Morbidity

Compared with minimal intervention Controlled cord traction may be more effective at reducing the risk of placental tissue retention at 30 minutes, but not at 60 minutes. We don't know whether controlled cord contraction plus oxytocin and uterine massage is more effective than oxytocin alone at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL) (low-quality evidence).

Controlled cord traction plus immediate cord drainage compared with expectant management We don't know whether controlled cord traction plus immediate cord drainage is more effective at reducing the drop in haemoglobin levels (low-quality evidence).

Need for further interventions

Controlled cord traction plus immediate cord drainage compared with expectant management Controlled cord traction plus immediate cord drainage is no more effective at reducing the need for manual removal of the placenta. (high-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits: We found one systematic review [5] and three additional RCTs. [6] [7] [8]

Controlled cord traction versus minimal intervention:
The systematic review (search date not reported, 2 RCTs, 1905 women having vaginal deliveries) assessed the effectiveness of controlled cord traction alone versus minimal intervention. [5] The review found no RCTs. [5] The first additional RCT (1648 low-risk women in the third stage of labour at a maternity unit in Abu Dhabi, United Arab Emirates) compared controlled cord traction versus minimal intervention. [6] Both groups had early cord clamping and received oxytocin, although at different times (see comment). The RCT found no significant difference between interventions in the need for transfusion (1/827 [0.1%] with cord traction *v* 4/821 [0.5%] with minimal intervention; OR 0.25, 95% CI 0.01 to 2.33), and rates of shock (2/827 [0.2%] with cord traction *v* 8/821 [1.0%] with minimal intervention; OR 0.25, 95% CI 0.04 to 1.25). The RCT found that, compared with minimal intervention, controlled cord traction significantly decreased the risk of retained placental tissue at 30 minutes (12/827 [1%] with controlled cord traction *v* 37/821 [5%] with minimal interven-

tion; OR 0.31, 95% CI 0.15 to 0.63) and found a similar trend at 60 minutes (3/827 [0.4%] with cord traction *v* 9/821 [1.1%] with minimal intervention; OR 0.33, 95% CI 0.07 to 1.32), although the difference did not reach statistical significance. Similarly, cord traction significantly reduced the need for further medical treatment (19/827 [2%] with cord traction *v* 42/821 [5%] with minimal intervention; OR 0.44, 95% CI 0.24 to 0.78). These results should be interpreted with caution, because the timing and mode of oxytocin administration was different in the two groups (see comment). The second additional RCT (300 women having vaginal deliveries in a hospital in China) compared the effects on postpartum haemorrhage of: controlled cord traction plus uterine massage; normal saline; rectal carboprost; oxytocin alone; and oxytocin plus controlled cord traction plus uterine massage. [7] It found that controlled traction plus uterine massage significantly reduced blood loss compared with normal saline (estimated blood loss: 147 mL with controlled cord traction plus massage *v* 244 mL with saline, P less than 0.01; women with blood loss of greater than 500 mL: 2% with controlled cord traction plus massage *v* 8% with saline, P value not reported). In addition, it found reduced blood loss in women receiving oxytocin plus controlled cord traction plus uterine massage compared with women receiving oxytocin only (estimated blood loss: 120 mL with oxytocin plus controlled cord traction plus massage *v* 172 mL with oxytocin alone, P less than 0.01; women with blood loss of greater than 500 mL: 0% with oxytocin plus controlled cord traction plus massage *v* 5% with oxytocin, P value not reported).

Controlled cord traction plus immediate cord drainage versus expectant management:
The third additional RCT (477 low-risk women in France) compared controlled cord traction plus immediate cord drainage versus expectant management of delivery. [8] Neither group received an oxytocic agent. The RCT found that controlled cord traction plus immediate cord drainage significantly reduced the drop in haemoglobin compared with expectant management (median haemoglobin drop: 0.95 g/dL with cord traction plus drainage *v* 1.40 g/dL with expectant management; P = 0.0002). However, it found no significant difference between interventions in postpartum haemoglobin levels (11.2 g/dL with cord traction plus drainage *v* 10.9 g/dL with expectant management; P = 0.09), number of women with a postpartum haemoglobin level less than 10 g/dL (51/239 [21%] with cord traction plus drainage *v* 56/238 [24%] with expectant management; P = 0.07), the need for manual removal of the placenta (18/239 [8%] with cord traction plus drainage *v* 20/238 [8%] with expectant management; P = 0.13), or the need for transfusion (0 with cord traction plus drainage *v* 1 with expectant management; P = 0.50).

Harms: The review and additional RCTs did not report on maternal adverse effects. [5] [6] [7] [8]

Comment:

Controlled cord traction versus minimal intervention:
The cord-traction group received intramuscular oxytocin 10 IU at delivery of the anterior shoulder of the baby, whereas the control group had a continuous infusion after delivery of the placenta. [6]

Controlled cord traction plus immediate cord drainage versus expectant management:
The exact timing of cord drainage in the active group was not specified. [8]

Clinical guide:
Controlled cord traction can be used in any resource setting.

OPTION IMMEDIATE BREASTFEEDING

We found no clinically important results about the effects of immediate breastfeeding on postpartum haemorrhage.

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits: We found no systematic review or RCTs examining the effects of immediate breastfeeding on postpartum haemorrahge.

Harms: We found no RCTs

Comment: None.

Clinical guide:
Immediate breastfeeding is an attractive option in low-resource settings, and can reduce neonatal mortality. [9] However, there is insufficient evidence to judge whether it has an effect on reducing the risk of postpartum haemorrhage.

OPTION UTERINE MASSAGE

Morbidity

Uterine massage with active management compared with active management alone Intermittent uterine massage every 10 minutes for an hour is no more effective at reducing blood loss of at least 500 mL (high-quality evidence).

Need for further interventions
Uterine massage with active managment compared with active management alone Intermittent uterine massage every 10 minutes for an hour is more effective at reducing the need for an additional uterotonic agent (high-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits: We found no systematic review but found one RCT. [10] The RCT (200 women who delivered without obvious genital trauma) compared uterine massage every 10 minutes for 60 minutes plus routine active management (oxytocin 10 IU, iv or im) versus routine active management alone (oxytocin 10 IU, iv or im). [10] The RCT found that uterine massage significantly decreased measured blood loss at 30 minutes and 60 minutes compared with active management (at 30 minutes: 168.8 mL with massage *v* 210.4 mL with active management, mean difference –41.6, 95% CI –75.7 to –7.5, P = 0.017; at 60 minutes: 204.3 mL with massage *v* 281.7 mL with active management, mean difference –77.4, 95% CI –119.2 to –35.5, P less than 0.001). There was no significant difference between groups for postpartum hemorrhage (at least 500 mL) (4/98 [5%] with massage *v* 8/102 [7%] with active managment, RR 0.52, 95% CI 0.16 to 1.67), but uterine massage significantly reduced the need for administration of an additional uterotonic agent (5/98 [6%] with massage *v* 26/102 [25%] with active management, RR 0.20, 95% CI 0.08 to 0.50). [10]

Harms: The RCT gave no information on adverse effects. [10]

Comment: **Clinical guide:**
Uterine massage is frequently performed immediately after placental delivery. It is generally believed to help to contract the uterus and to decrease blood loss, but it can be uncomfortable for the woman. Given the small likelihood of harm, it is reasonable to include this in standard management given the single supportive study.

QUESTION What are the effects of drug interventions to prevent primary postpartum haemorrhage?

OPTION OXYTOCIN

Morbidity
Compared with placebo/no intervention Oxytocin may be more effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL, or of at least 1000 mL, but we don't know whether it is more effective at reducing the rate of drop in maternal haemoglobin levels postpartum (low-quality evidence).

Compared with ergot compounds Oxytocin and ergot alkaloids are equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL, or of at least 1000 mL (moderate-quality evidence).

Oxytocin compared with oxytocin plus ergometrine combinations Oxytocin alone is less effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL, but is associated with less adverse effects, such as diastolic hypertension, nausea, and vomiting (moderate-quality evidence).

Compared with oral misoprostol Oxytocin and oral misoprostol seem equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL, or of at least 1000 mL. However, oral misoprostol is more likely to increase adverse effects, particularly fever, shivering, and diarrhoea (moderate-quality evidence).

Compared with sublingual misoprostol Oxytocin and sublingual misoprostol are equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL, or of at least 1000 mL (moderate-quality evidence).

Compared with rectal misoprostol Oxytocin and rectal misoprostol are equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL, or of at least 1000 mL (high-quality evidence).

Compared with prostaglandin E2 compounds We don't know whether oxytocin is more effective than sulprostone at reducing blood loss (low-quality evidence).

Need for further interventions
Compared with placebo/no intervention Oxytocin may be more effective at reducing the need for additional medical treatment of postpartum haemorrhage (low-quality evidence).

Compared with ergot compounds Oxytocin is more effective at reducing the need for manual removal of the placenta, but oxytocin and ergot compounds are equally effective at reducing the need for additional medical treatment of postpartum haemorrahge (moderate-quality evidence).

Compared with oxytocin plus ergometrine combinations Oxytocin alone and oxytocin plus ergometrine combinations are equally effective at reducing the need for manual removal of the placenta and the need for transfusion. We don't know whether oxytocin plus ergometrine combinations is more effective at reducing the need for additional medical treatment of postpartum haemorrhage (moderate-quality evidence).

Compared with oral misoprostol Oxytocin and oral misoprostol seem equally effective at reducing the need for manual removal of the placenta and the need for blood transfusions. However, oral misoprostol seems to reduce the need for additional uterotonics (moderate-quality evidence).

Compared with sublingual misoprostol Oxytocin and sublingual misoprostol are equally effective at reducing the need for additional oxytocics (moderate-quality evidence).

Compared with rectal misoprostol Oxytocin and rectal misoprostol are equally effective at reducing the need for blood transfusion, but we don't know whether rectal misoprostol is more effective at reducing the need for additional uterotonics (moderate-quality evidence).

Mortality

Compared with oral misoprostol Oxytocin and oral misoprostol seem equally effective at reducing mortality (high-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits:

Oxytocin versus placebo/no intervention:

We found one systematic review (search date 2004) and one subsequent RCT. [11] [12] The systematic review identified five RCTs and two quasi-RCTs comparing oxytocin versus placebo or no intervention, with oxytocin given by different routes (im in 2 RCTs and 1 quasi-randomised trial; iv in 3 RCTs and 1 quasi-randomised trial) and in a variety of doses (ranging from 3 to 10 IU). In two RCTs, oxytocin was used in conjunction with expectant management, in one trial with active management, and in the other trials the context was not defined. Two trials were in the USA, three were in Europe (Sweden, France, and the Netherlands), and one was in Singapore. Two studies specified that the participants were low risk; the others did not specify. The review found that oxytocin significantly reduced the need for additional medical treatment of postpartum haemorrhage compared with placebo or no intervention (4 RCTs and 1 quasi-randomised trial, 2327 women: RR 0.50, 95% CI 0.39 to 0.64, absolute figures not reported). Similarly, the review found that oxytocin significantly reduced measures of blood loss, such as postpartum haemorrhage (defined as clinically estimated blood loss at least 500 mL, 5 RCTs and 1 quasi-randomised trial, 3193 women: 188/1582 [12%] with oxytocin *v* 391/1611 [24%] with placebo/no intervention; RR 0.50, 95% CI 0.43 to 0.59), severe postpartum haemorrhage (defined as clinically estimated blood loss at leat 1000 mL, 3 RCTs and 1 quasi-randomised trial, 2243 women: 48/1107 [4%] with oxytocin *v* 83/1136 [7%] with placebo/no intervention; RR 0.61, 95% CI 0.44 to 0.87), and mean blood loss (3 RCTs and 1 quasi-randomised trial, 1373 women: –102 mL, 95% CI –135 mL to –59 mL).Oxytocin also reduced the rate of maternal postpartum haemoglobin less than 9 g/dL, although the difference did not reach statistical significance (1 RCT, 933 women: 20/485 [4%] with oxytocin *v* 30/458 [7%] with placebo/no intervention; RR 0.63, 95% CI 0.36 to 1.09). In a subgroup analysis comparing oxytocin after expectant management of the third stage of labour versus expectant management alone, the review found that oxytocin significantly reduced the risk of postpartum haemorrhage (129/591 [22%] with oxytocin after expectant management *v* 230/630 [37%] with expectant management alone; RR 0.61, 95% CI 0.51 to 0.73) and the need for additional therapeutic uterotonics (54/591 [9%] with oxytocin after expectant management *v* 93/630 [15%] with expectant management alone; RR 0.66, 95% CI 0.48 to 0.90). It also decreased the risk of severe postpartum haemorrhage (39/591 [7%] with oxytocin after expectant management *v* 59/630 [9%] with expectant management alone; RR 0.73, 95% CI 0.49 to 1.07) and postpartum haemoglobin level less than 9 g/dL (20/485 [4%] with oxytocin after expectant management *v* 30/458 [7%] with expectant management alone; RR 0.63, 95% CI 0.36 to 1.09), although the differences did not reach significance. The review found no significant difference between interventions in the need for blood transfusion (9/591 [2%] with oxytocin *v* 8/630 [1%] with placebo/no intervention; RR 1.30, 95% CI 0.50 to 3.39) and for manual placenta removal (19/619 [3%] with oxytocin *v* 11/654 [2%] with placebo/no intervention; RR 1.67, 95% CI 0.82 to 3.41). The review did not report on the need for additional surgical treatment, maternal mortality, serious maternal morbidity, Sheehan's syndrome, or uterine inversion. The subsequent RCT (130 women in Tunisia expecting single uncomplicated, full-term vaginal deliveries) compared oxytocin (5 IU at time of delivery) versus no oxytocin. [12] All women recieved immediate cord clamping and controlled cord traction. The RCT found that postpartum anaemia (haemoglobin less than 10 g/dL) was significantly less frequent among women given oxytocin compared with no oxytocin (17/65 [26%] with oxytocin *v* 29/65 [45%] with no oxytocin, OR 0.44, 95% CI 0.21 to 0.92). The RCT found that oxytocin significantly improved mean haemoglobin drop compared with no oxytocin (0.51 ± 1.23 g m/dL with oxytocin *v* 1.20 ± 1.30 g m/dL with no oxytocin, mean difference –0.69 gm/dL, 95% CI –1.13 g/dL to –0.25 g/dL), and that the third stage of labour was significantly shorter for the oxytocin group

compared with no oxytocin (2.5 ± 4.3 minutes with oxytocin *v* 10.6 ± 5.0 minutes withy no oxytocin, difference –8.1 minutes, 95 % CI –9.7 minutes to –6.5 minutes). One woman in each group required manual placenta removal. [12]

Oxytocin versus ergot compounds:
We found one systematic review (search date 2004) [11] and two additional RCTs [13] [14] comparing oxytocin versus ergometrine. The systematic review identified five RCTs and one quasi-randomised trial including 2869 women, and used a wide variety of oxytocin doses (2–10 IU) and modes of administration (im in 1 RCT; iv in 3 RCTs and 1 quasi-randomised trial; combined im plus iv routes in 1 RCT). There were two different ergot alkaloids (ergometrine and methylergonovine maleate, used in at least 4 different doses ranging from 0.2–4 mg). Three studies were in the USA, two were in Europe (the Netherlands and Sweden), and one was in Singapore. One specified that the women were low risk, four did not specify, and one had no exclusion criteria. The review found that oxytocin significantly reduced the need for manual placenta removal compared with ergometrine (2 RCTs and 1 quasi-randomised trial, 1747 women: 66/908 [7%] with oxytocin *v* 70/838 [8%] with ergometrine; RR 0.57, 95% CI 0.41 to 0.79). However, it found no significant difference between interventions in the need f.or additional medical treatment of postpartum haemorrhage (2 RCTs, 984 women: 35/557 [6%] with oxytocin *v* 46/651 [7%] with ergometrine; RR 1.02, 95% CI 0.67 to 1.55) and in measures of blood loss, such as postpartum haemorrhage (4 RCTs and 1 quasi-randomised trial, 2719 women: 88/1383 [6%] with oxytocin *v* 127/1336 [10%] with ergometrine; RR 0.90, 95% CI 0.70 to 1.16), severe postpartum haemorrhage (2 RCTs and 1 quasi-randomised trial, 1746 women: 20/908 [2%] with oxytocin *v* 27/838 [3%] with ergometrine; RR 0.99, 95% CI 0.56 to 1.74), or mean blood loss (2 trials, 1373 women: –29 mL, 95% CI –69 mL to +1 mL). One RCT identified by the review found a higher need for blood transfusion with oxytocin, although the number of events was small and the confidence interval wide (1 RCT: 2/78 [3%] with oxytocin *v* 1/146 [1%] with ergometrine; RR 3.74, 95% CI 0.34 to 40.64). The review did not report on the need for additional surgical treatment, maternal mortality, serious maternal morbidity, anaemia, Sheehan's syndrome, uterine inversion, or retained placental tissue. The first additional RCT (88 primigravid women of unspecified risk with vertex presentation in the UK) compared intravenous oxytocin 10 IU versus intravenous ergometrine 0.5 mg. [13] It found similar results in measured blood loss in both groups (201 mL with ergometrine *v* 208 mL with oxytocin; significance assessment not performed). It did not report on transfusion, need for further medical management, retained placenta, or serious maternal morbidity. The second RCT (2023 women as part of a 3-arm trial in Velore, India, with a number of medical pregnancy problems excluded) compared intramuscular oxytocin 10 IU versus intravenous ergotamine 2 mg. [14] It found no differences in blood loss (183 mL for oxytocin *v* 188 mL for ergometrine), use of additional oxytocic agents (6% *v* 8%), blood loss greater than 500 mL (2% *v* 3%), blood loss greater than 1000 mL (0.65% *v* 0.89%), retained placenta (0.8% *v* 0.7%), or blood transfusion (0.32% *v* 0.44%). The RCT did not perform post hoc comparisons, but overall significance tests reported no significant difference between groups.

Oxytocin versus oxytocin plus ergometrine combinations:
We found one systematic review (search date 2004) comparing oxytocin versus combined oxytocin plus ergot alkaloid preparations. [15] See benefits of oxytocin plus ergometrine combinations, p 12 .

Oxytocin versus oral misoprostol:
See benefits of oral misoprostol, p 17 .

Oxytocin versus sublingual misoprostol:
See benefits of sublingual misoprostol, p 16 .

Oxytocin versus rectal misoprostol:
See benefits of rectal misoprostol, p 19 .

Oxytocin versus prostaglandin E2 compounds:
See benefits of prostaglandin E2 compounds, p 15 .

Harms:

Oxytocin versus placebo/no intervention:
The systematic review found no significant difference between interventions in the need for manual removal of the placenta (3 RCTs and 1 quasi-randomised trial, 2243 women; 51/1107 [5%] with oxytocin *v* 43/1136 [4%] with placebo/no intervention; RR 1.17, 95% CI 0.79 to 1.73), rate of transfusion (2 RCTs, 1221 women: 9/591 [2%] with oxytocin *v* 8/630 [1%] with placebo/no intervention; RR 1.30, 95% CI 0.50 to 3.39), or nausea between delivery of the baby and discharge from the labour ward (1 RCT, 52 women: 0/28 [0%] with oxytocin *v* 1/24 [4%] with placebo/no intervention; RR 0.29, 95% CI 0.01 to 6.74). [11] The subsequent RCT gave no information on adverse effects. [12]

Oxytocin versus ergot compounds:
The systematic review found no significant difference between interventions in postpartum hypertension (diastolic blood pressure greater than 100 mm Hg between delivery of baby and discharge from labour ward, 1 RCT, 150 women: 4/50 [8%] with oxytocin *v* 15/100 [15%] with ergometrine; RR 0.53, 95% CI 0.19 to 1.52). [11] The first additional RCT found significantly less nausea with oxytocin compared with ergometrine (0/44 [0%] with oxytocin *v* 6/44 [14%] with ergometrine; P less than 0.01). [13] The second RCT noted no differences in mild or moderate nausea (2% with oxytocin *v*1% with ergometrine), vomiting (0.3% with oxytocin *v* 0.4% with ergometrine), shivering (2% with oxytocin *v* 4% with ergometrine), diarrhoea (0% with oxytocin *v* 0.3% with ergometrine) and headache (0.2% with oxytocin *v* 0.3% with ergometrine). Again, although no post hoc comparisons were performed, analysis across the three arms revealed no significant difference between the groups. [14]

Oxytocin versus oxytocin plus ergometrine combinations:
See harms of oxytocin plus ergometrine combinations, p 12 .

Oxytocin versus oral misoprostol:
See harms of oral misoprostol, p 17 .

Oxytocin versus sublingual misoprostol:
See harms of sublingual misoprostol, p 16 .

Oxytocin versus rectal misoprostol:
See harms of rectal misoprostol, p 19 .

Oxytocin versus prostaglandin E2 compounds:
See harms of prostaglandin E2 compounds, p 15 .

Comment:

Clinical guide:
Oxytocin, either alone or in combination with ergometrine, should be used for the prevention of postpartum haemorrhage. Oxytocin by itself may be preferable to the combination with ergot compounds, because differences in efficacy are likely to be small if any, and oxytocin alone seems to have fewer adverse effects. Both drugs are inexpensive and can be given intramuscularly, making them useful in any resource setting. One limitation is that oxytocics, and especially ergometrine, deteriorate rapidly in tropical conditions.

OPTION CARBOPROST INJECTION

Morbidity
Compared with ergot compounds Carboprost and methylergometrine are equally effective at reducing the proportion of women with postpartum haemorrhage defined as blood loss of at least 500 mL (high-quality evidence).

Compared with oxytocin plus ergometrine combination Carboprost and a fixed combination of oxytocin and ergometrine are equally effective at reducing blood loss (moderate-quality evidence).

Compared with rectal misoprostol Carboprost injection and rectal misoprostol are equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL. However, rectal misoprostol causes more side effects such as nausea, vomiting, diarrhoea, and shivering (moderate-quality evidence).

Need for further interventions
Compared with rectal misoprostol Carboprost injection is less likely to increase the need for additional oxytocics (high-quality evidence).

Note
We found no direct information about the effects of carboprost injection compared with no active treatment or no treatment in women with postpartum haemorrhage. Carboprost has been associated with unacceptable gastrointestinal effects particularly diarrhoea and nausea.

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits:

Carboprost injection versus placebo/no intervention:
We found no systematic review or RCTs.

Carboprost injection versus ergot compounds:
We found one systematic review (search date 2007) [16] which identified two RCTs comparing carboprost injection versus ergot compounds, [17] [18] and one additional RCT. [19] The first RCT included in the review (150 low-risk women in Egypt) compared carboprost trometamol (250 micro-

grams im) versus methylergometrine (0.2 mg iv) and found no instances of postpartum haemorrhage (estimated blood loss at least 500 mL) with either intervention. [17] The second RCT included in the review (80 women with at least 1 risk factor for postpartum haemorrhage, delivering after 28 weeks' gestation) compared carboprost (250 micrograms im) versus methylergometrine (0.2 mg iv). [18] It found that carboprost significantly decreased blood loss in the third stage and fourth stages of labour (third stage: 113 mL with carboprost *v* 202 mL with methylergometrine; P less than 0.001; fourth stage: 47 mL with carboprost *v* 67 mL with methylergometrine; P less than 0.001). It found no significant difference between interventions in the proportion of women with postpartum haemorrhage (2/40 [5%] with carboprost *v* 3/40 [8%] with methylergometrine; P = 1.0). [18] The additional RCT (215 women) compared carboprost tromethamine (250 micrograms) versus intravenous methylergometrine (dose not stated). [19] The RCT found no significant difference in the proportion of women who had postpartum haemorrhage between carboprost and methyergotamine (5/107 [5%] with carboprost *v* 7/108 [7%] with methylergometrine; RR 0.72, 95% CI 0.24 to 2.20) or in measured blood loss (mean 235.7 mL with carboprost *v* 214.1 mL with methylergometrine, mean difference 21.6 mL, 95% CI –6.5 mL to +49.8 mL). The RCT found that carboprost tromethamine did not significantly reduce duration of the third stage of labour (4.3 minutes with carboprost *v* 3.9 minutes methylergometrine, P = 0.038) compared with methylergometrine. The RCT found no significant difference between groups in postpartum haemoglobin or haematocrit levels (no further data reported, reported as non-significant). [19]

Carboprost injection versus oxytocin plus ergometrine combination:
We found one systematic review (search date 2007) [16] and one additional RCT. [20] The one RCT [21] identified by the review [16] compared 15-methyl prostaglandin F2 alpha (125 micrograms im) versus a fixed combination of oxytocin 0.5 mg plus ergometrine. [21] It found no significant difference between interventions in measures of blood loss, haemoglobin change, the need for additional oxytocic agents, or manual removal of the placenta. The additional RCT (529 women in the UK) compared carboprost (250 micrograms im) versus a fixed combination of oxytocin plus ergometrine (1 ampoule). [20] It found similar measures of blood loss between intramuscular prostaglandin and oxytocin plus ergometrine (43/263 [16%] with prostaglandin *v* 30/266 [11%] with oxytocin plus ergometrine; RR 1.45, 95% CI 0.94 to 2.24). The RCT was terminated early at the time of interim analysis because of unacceptable gastrointestinal adverse effects in the prostaglandin group (see harms below). At the time of termination, there was no suggestion of a difference in effectiveness between the study groups.

Carboprost injection versus rectal misoprostol:
See benefits of rectal misoprostol, p 19 .

Harms:

Carboprost injection versus placebo/no intervention:
We found no RCTs or SRs.

Carboprost injection versus methylergometrine injection:
The first RCT found a significantly higher rate of vomiting with the injectable prostaglandin compared with the ergot compound (16% with injectable prostaglandin *v* 1% with ergot compound; RR 12.7, 95% CI 1.7 to 94.9). [17] It also found a higher risk of abdominal pain and of diarrhoea with the injectable prostaglandin (abdominal pain: 8% with injectable prostaglandin *v* 0% with ergot compound; RR 13.70, 95% CI 0.79 to 239.00; diarrhoea: 3% with injectable prostaglandin *v* 0% with ergot compound; RR 5.27, 95% CI 0.26 to 108.00); both confidence intervals were wide and compatible with a large increase. The second RCT also found a higher proportion of women with diarrhoea with carboprost compared with methylergometrine, although the difference did not reach statistical significance (17% with carboprost *v* 0% with methylergometrine; P = 0.01). [18] The additional RCT noted a 1% incidence of transient hypertension in the methyl ergometrine group, and a 20% incidence of diarrhoea in the carboprost-tromethamine group (no significance assessment performed). [19]

Carboprost injection versus oxytocin plus ergometrine combination:
The RCT identified by the review found that the injectable carboprost significantly increased the risk of diarrhoea compared with a fixed combination of oxytocin plus ergometrine (16/54 [30%] with prostaglandin *v* 1/58 [2%] with oxytocin plus ergometrine; P less than 0.005). [21] The additional RCT was terminated early because of gastrointestinal adverse effects with the injectable carboprost (27% with prostaglandin *v* 6% with oxytocin plus ergometrine), particularly diarrhoea (21% with prostaglandin *v* 1% with oxytocin plus ergometrine) and nausea (4% with prostaglandin *v* 1% with oxytocin plus ergometrine). [20] No significance assessment was performed for either of the interim results.

Carboprost injection versus rectal misoprostol:
See harms of rectal misoprostol, p 19 .

Comment: **Clinical guide:**
Data on injectable carboprost are limited, but it is clearly no better than oxytocin, ergot compounds, or combinations, and has more adverse effects.

OPTION ERGOT COMPOUNDS (ERGOMETRINE/METHYLERGOTAMINE)

Morbidity

Ergot compounds compared with placebo/no intervention Intravenous and intramuscular ergot compounds are more effective at reducing postpartum haemorrhage defined as blood loss of 500 mL or of at least 1000 mL, and at improving postpartum haemoglobin levels, but are associated with an increased risk of vomiting, elevated blood pressure, and pain (moderate-quality evidence).

Compared with oxytocin Oxytocin and ergot alkaloids are equally effective at reducing postpartum haemorrhage defined as blood loss of 500 mL or of at least 1000 mL (moderate-quality evidence).

Compared with oxytocin plus ergometrine combinations Ergot compounds and oxytocin plus ergometrine combinations are equally effective at reducing postpartum haemorrhage defined as blood loss of 500 mL or of at least 1000 mL (moderate-quality evidence).

Compared with oral misoprostol Ergot compounds and oral misoprostol are equally effective at reducing postpartum haemorrhage defined as blood loss of 500 mL or of at least 1000 mL. However, oral misoprostol increases the risk of shivering and fever (high-quality evidence).

Compared with sublingual misoprostol Sublingual misoprostol and ergometrine are equally effective at reducing postpartum haemorrhage defined as blood loss of 500 mL or of at least 1000 mL, but ergometrine increases the risk of shivering (high-quality evidence).

Compared with carboprost Methylergometrine and carboprost are equally effective at reducing the proportion of women with postpartum haemorrhage defined as blood loss of at least 500 mL (high-quality evidence).

Need for further interventions

Ergot compounds compared with placebo/no intervention Ergot compounds are more effective at reducing the need for additional uterotonics, but not at reducing the need for manual removal of the retained placenta (moderate-quality evidence).

Compared with oxytocin Ergot compounds are less effective at reducing the need for manual removal of the placenta, but ergot compounds and oxytocin are equally effective at reducing the need for additional medical treatment of postpartum haemorrhage (moderate-quality evidence).

Compared with oxytocin plus ergometrine combinations Ergot compounds and oxytocin plus ergometrine combinations are equally effective at reducing the need for manual removal of the placenta and the need for transfusion (moderate-quality evidence).

Compared with oral misoprostol Ergot compounds and oral misoprostol are equally effective at reducing the need for manual removal of the placenta, and the need for additional uterotonics or blood transfusion (high-quality evidence).

Compared with sublingual misoprostol Ergometrine and sublingual misoprostol are equally effective at reducing the need for manual removal of the placenta, and for additional medical treatment (high-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits: **Ergot compounds versus placebo/no intervention:**
We found one systematic review comparing ergot compounds versus placebo or no intervention.[22] The systematic review (search date 2007) included six RCTs (3941 women), all conducted in resource-rich countries. Three RCTs compared ergot compound versus placebo and three RCTs compared ergot compound versus no treatment. The RCTs included in the review used a variety of doses and routes of administration of ergometrine or methylergonovine. Four RCTs administered the drug intravenously, one RCT intramuscularly, and one RCT orally. The intravenous and intramuscular doses ranged from 0.2 to 0.5 mg. The oral dose was 0.4 mg. The review found that intravenous or intramuscular ergot alkaloids significantly decreased mean blood loss, and significantly reduced the risk of postpartum haemorrhage compared with placebo or no treatment (mean blood loss: 2 RCTs, 2429 women; WMD –83.0 mL, 95% CI –99.4 mL to –66.7 mL; postpartum harmorrhage at least 500 mL, 3 RCTs, 3409 women, RR 0.38, 95% CI 0.21 to 0.69, absolute numbers not reported). One RCT included in the review also found that ergot compound significantly reduced the risk of postpartum haemorrhage (at least 1000 mL, 1429 women, RR 0.09, 95% CI 0.01 to 0.72, no absolute numbers reported), significantly increased postpartum haemoglobin less than 10 g/dL (RR 0.30, 95% CI 0.14 to 0.67) and significantly increased mean haemoglobin at 48–72 hours

postpartum (WMD 0.50 g/dL, 95% CI 0.38 g/dL to 0.62 g/dL, no absolute numbers reported) compared with placebo. The review found no significant difference in risk of retained placenta or need for manual removal between groups (2 RCTs, 1429 women, RR 3.75, 95% CI 0.14 to 99.7, no absolute numbers reported). There was also no significant difference in blood transfusion (2 RCTs, 1579 people, RR 0.34, 95% CI 0.05 to 2.16) for ergot compounds compared with placebo. However the review found that ergot compunds significantly reduced the need for additional uterotonic administration compared with placebo or no treatment (2 RCTs, 2409 people, RR 0.25, 95% CI 0.10 to 0.66, absolute numbers not reported). [22]

Ergot compounds versus oxytocin:
See benefits of oxytocin, p 6 .

Ergot compounds versus oxytocin plus ergometrine combinations:
See benefits of oxytocin plus ergometrine combinations, p 12 .

Ergot compounds versus oral misoprostol:
See benefits of oral misoprostol, p 17 .

Ergot compounds versus sublingual misoprostol:
See benefits of sublingual misoprostol, p 16 .

Ergot compounds versus carboprost:
See benefits of carboprost, p 9 .

Harms:

Ergot compounds versus placebo/no intervention:
The systematic review found that ergot compounds significantly increased risk of vomiting (2 RCTs, 1579 people, RR 11.81, 95% CI 1.78 to 78.28, absolute numbers not reported), elevated blood pressure (3 RCTs, 1559 people, RR 2.60, 95% CI 1.03 to 6.57), and pain after birth requiring pain medication (1 RCT, 1429 people, RR 2.53, 95% CI 1.34 to 4.78) compared with placebo or no treatment. Two RCTs (1579 people) found no significant difference in nausea (RR 8.63, 95% CI 0.26 to 284.55, no absolute numbers reported), headache (RR 3.93, 95% CI 0.51 to 30.50, no absolute numbers reported), and eclampsia (RR 3.34, 95% CI 0.38 to 29.43, no absolute numbers reported) between ergot compounds and placebo or no treatment. [22]

Ergot compounds versus oxytocin:
See harms of oxytocin, p 6 .

Ergot compounds versus oxytocin plus ergometrine combinations:
See harms of oxytocin plus ergometrine combinations, p 12 .

Ergot compounds versus oral misoprostol:
See harms of oral misoprostol, p 17 .

Ergot compounds versus sublingual misoprostol:
See harms of sublingual misoprostol, p 16 .

Ergot compounds versus carboprost:
See harms of carboprost, p 9 .

Comment:

Clinical guide:
Ergot compounds are clearly effective in preventing postpartum haemorrhage, but are associated with significant adverse effects. They may be administered intravenously or intramuscularly, but there is no supportive evidence for oral administration being effective. They may be administered in combination with oxytocin (syntometrine). They should be administered when no other uterotonic is available, but given the adverse-effect profile, and similar effectiveness to oxytocin, oxytocin is the preferred agent when available.

OPTION OXYTOCIN PLUS ERGOMETRINE

Morbidity
Compared with ergot compounds alone Oxytocin plus ergometrine combinations and ergot compounds are equally effective at reducing postpartum haemorrhage defined as blood loss of 500 ml or 1000 ml or greater (moderate-quality evidence).

Compared with oxytocin alone Oxytocin plus ergometrine combinations are more effective at reducing postpartum haemorrhage defined as blood loss of 500 ml or greater but are associated with increased rates of adverse effects such as diastolic hypertension, nausea, and vomiting (moderate-quality evidence).

Compared with carboprost Oxytocin plus ergometrine combinations and carboprost are equally effective at reducing blood loss but carboprost is associated with unacceptable gastrointestinal effects (moderate-quality evidence).

Compared with sublingual misoprostol We don't know whether oxytocin and ergometrine combinations are more effective at reducing blood loss but are less likely to increase the risk of shivering and fever (low-quality evidence).

Compared with oral misoprostol We don't know whether oxytocin plus ergometrine combinations are more effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL or at least 1000 mL. However, oral misoprostol increases the risk of shivering (moderate-quality evidence).

Compared with rectal misoprostol We don't know whether oxytocin plus ergometrine combinations are more effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL, but it is more effective at reducing severe postpartum haemorrhage defined as blood loss of at least 1000 mL (moderate-quality evidence).

Need for further interventions

Compared with ergot compounds alone Oxytocin plus ergometrine combinations and ergot compounds are equally effective at reducing the need for manual removal of the placenta and the need for transfusion (moderate-quality evidence).

Compared with oxytocin alone Oxytocin plus ergometrine combinations and oxytocin alone are equally effective at reducing the need for manual removal of the placenta and the need for transfusion. We don't know whether oxytocin plus ergometrine combinations are more effective at reducing the need for additional medical treatment of postpartum haemorrhage (moderate-quality evidence).

Compared with oral misoprostol Oxytocin and ergometrine combinations seem less effective at reducing the need for additional uterotonics, but we don't know whether they are more effective at reducing the need for manual removal of the placenta. However oral misoprostol and oxytocin/ergometrine combinations are equally effective at reducing the need for blood transfusion (moderate-quality evidence).

Compared with rectal misoprostol Oxytocin plus ergometrine combinations are more likely to decrease the need for additional uterotonics (high-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits:

Oxytocin plus ergometrine combinations versus ergot compounds alone:

We found one systematic review (search date 2004) comparing oxytocin plus ergometrine combinations versus ergot alkaloids alone. [11] The review identified four RCTs and one controlled trial including a total of 2891 women. The combination consisted of oxytocin 5 IU plus ergometrine 0.5 mg (given im in all but 1 RCT, where it was given iv), whereas the ergot comparison contained ergometrine in three RCTs, ergometrine maleate in one RCT, and methergine in one controlled trial, with doses varying from 0.1–0.5 mg, and administration being intravenous in one RCT and one controlled trial, intramuscular in one RCT, and both in two RCTs. Two studies were in the UK, one in Australia, one in Singapore, and one in Finland. The review reported that two were in low-risk populations and did not specify regarding the other three. The review found no significant difference between interventions in outcomes assessing blood loss, such as risk of postpartum haemorrhage (estimated blood loss greater than 500 mL, 4 RCTs and 1 controlled trial, 2891 women: 66/1427 [5%] with oxytocin plus ergometrine *v* 52/1464 [4%] with ergot compounds; RR 1.29, 95% CI 0.90 to 1.84) or severe postpartum haemorrhage (estimated blood loss greater than 1000 mL, 1 controlled trial, 1120 women: 5/560 [0.9%] with oxytocin plus ergometrine *v* 3/560 [0.5%] with ergot compounds; RR 1.67, 95% CI 0.40 to 6.94), or need for transfusion (1 controlled trial, 1120 women: 5/560 [0.9%] with oxytocin plus ergometrine *v* 7/560 [1%] with ergot compounds; RR 0.71, 95% CI 0.23 to 2.24). Similarly, it found no significant difference in the need for manual removal of the placenta (1 RCT and 1 controlled trial, 1927 women: 13/951 [1%] with oxytocin plus ergometrine *v* 13/976 [1%] with ergot compounds; RR 1.02, 95% CI 0.48 to 2.20). The review gave no information on outcomes such as maternal mortality, serious maternal morbidity, need for surgical management, Sheehan's syndrome, symptomatic anaemia, or uterine inversion.

Oxytocin plus ergometrine combinations versus oxytocin alone:

We found one systematic review (search date 2004) comparing oxytocin versus combined oxytocin plus ergot alkaloid preparations. [15] The review identified five RCTs and one controlled trial including a total of 9332 women. Women in the oxytocin group received doses of 5 IU (2 trials) or 10 IU (4 trials), whereas all women in the combination group received oxytocin 5 IU plus ergometrine 0.5 mg intramuscularly. Additionally, all women had active management of the third stage of labour. One study was conducted in the United Arab Emirates, one in Australia, two in Hong Kong, one in the UK, and one in Sweden. Four populations seemed to be low risk, and two were not specified. The review found that, compared with oxytocin alone, women receiving the combination had a significantly lower risk of postpartum haemorrhage (any dose of oxytocin, 5 RCTs and 1 controlled trial,

9332 women: 392/4661 [8%] with oxytocin plus ergometrine *v* 469/4671 [10%] with oxytocin, OR 0.82, 95% CI 0.71 to 0.95; 5 IU oxytocin, 1 RCT and 1 controlled trial, 1839 women: 11/919 [1%] with oxytocin plus ergometrine *v* 26/920 [3%] with oxytocin, OR 0.43, 95% CI 0.23 to 0.83; 10 IU oxytocin, 4 RCTs, 7493 women: 372/3742 [10%] with oxytocin plus ergometrine *v* 432/3751 [12%] with oxytocin, OR 0.85, 95% CI 0.73 to 0.98) and a lower risk of severe postpartum haemorrhage, although this difference did not reach statistical significance (5 RCTs and 1 controlled trial, 9332 women: 86/3972 [2%] with oxytocin plus ergometrine *v* 111/3982 [3%] with oxytocin; OR 0.78, 95% CI 0.58 to 1.03). In addition, the review found that the oxytocin plus ergometrine combination significantly reduced the need for additional medical treatment of postpartum haemorrhage compared with oxytocin alone (10 IU oxytocin, 3 RCTs, 5465 women: 397/2726 [15%] with oxytocin plus ergometrine *v* 466/2739 [17%] with oxytocin; OR 0.83, 95% CI 0.72 to 0.96). However, significant heterogeneity existed between the RCTs for this outcome, and when the analysis was repeated with a random-effects model, there was no significant difference between interventions (OR 0.87, 95% CI 0.58 to 1.32, absolute figures not reported). The review found no significant difference in need for manual removal of the placenta (10 IU oxytocin, 5 RCTs and 1 controlled trial, 9332 women: 130/4661 [3%] with oxytocin plus ergometrine *v* 127/4671 [3%] with oxytocin; OR 1.03, 95% CI 0.80 to 1.33) or for blood transfusion (10 IU oxytocin, 4 RCTs, 7482 women: 49/3725 [1%] with oxytocin plus ergometrine *v* 36/3747 [1%] with oxytocin; OR 1.37, 95% CI 0.89 to 2.10). The review did not report on outcomes such as the need for additional surgical treatment, maternal mortality, serious maternal morbidity, symptomatic anaemia, Sheehan's syndrome, uterine inversion, or retained placental tissue.

Oxytocin plus ergometrine combinations versus carboprost:
See benefits of carboprost, p 9 .

Oxytocin plus ergometrine combinations versus prostaglandin E2 compounds:
See benefits of prostaglandin E2 compounds, p 15 .

Oxytocin plus ergometrine combinations versus sublingual misoprostol:
See benefits of sublingual misoprostol, p 16 .

Oxytocin plus ergometrine combinations versus oral misoprostol:
See benefits of oral misoprostol, p 17 .

Oxytocin plus ergometrine combinations versus rectal misoprostol:
See benefits of rectal misoprostol, p 19 .

Harms:

Oxytocin plus ergometrine combinations versus ergot compounds:
The systematic review reported no adverse effects. [11]

Oxytocin plus ergometrine combinations versus oxytocin:
The review found that oxytocin plus ergometrine combinations significantly increased diastolic blood pressure compared with oxytocin alone (OR 2.81, 95% CI 1.17 to 6.73, absolute figures not reported). [15] Similarly, the review found that the combination significantly increased the risk of vomiting (3 RCTs, 5458 women: 373/2721 [14%] with oxytocin plus ergometrine *v* 66/2737 [2%] with oxytocin; OR 4.92, 95% CI 4.03 to 6.00), nausea (3 RCTs, 5458 women: 487/2721 [18%] with oxytocin plus ergometrine *v* 128/2737 [5%] with oxytocin; OR 4.07, 95% CI 3.43 to 4.84), and nausea and vomiting combined (4 RCTs, 7477 women: 874/3737 [23%] with oxytocin plus ergometrine *v* 198/3749 [5%] with oxytocin; OR 5.71, 95% CI 4.97 to 6.57) compared with oxytocin alone.

Oxytocin plus ergometrine combinations versus Carboprost:
See harms of carboprost, p 9 .

Oxytocin plus ergometrine combinations versus prostaglandin E2 compounds:
See harms of prostaglandin E2 compounds, p 15 .

Oxytocin plus ergometrine combinations versus sublingual misoprostol:
See harms of sublingual misoprostol, p 16 .

Oxytocin plus ergometrine combinations versus oral misoprostol:
See harms of oral misoprostol, p 17 .

Oxytocin plus ergometrine combinations versus rectal misoprostol:
See harms of rectal misoprostol, p 19 .

Comment: All studies used a fixed combination of oxytocin plus ergometrine as a prepared mixture (one ampoule containing oxytocin 5 IU plus ergometrine 0.5 mg).

Oxytocin plus ergometrine combinations versus oxytocin:
All four RCTs (7477 women) reporting elevated blood pressure as outcome gave oxytocin 10 IU in the control arm. [15] In spite of varying definitions of elevated blood pressure, and significant heterogeneity between studies, the authors still found a significant effect when applying a random-effects model.

OPTION PROSTAGLANDIN E2 COMPOUNDS

Morbidity
Sulprostone compared with placebo Sulprostone is no more effective at reducing postpartum haemorrhage defined as blood loss of greater than 500 mL or greater than 1000 mL (moderate-quality evidence).

Compared with oxytocin We don't know whether sulprostone is more effective at reducing blood loss (low-quality evidence).

Need for further interventions
Sulprostone compared with placebo Sulprostone is no more effective at reducing the need for further medical treatment for postpartum haemorrhage (moderate-quality evidence).

Note
We found no direct information about the effects of dinoprostone.

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits:

Sulprostone injection versus placebo:
We found one systematic review (search date 2007), which identified one RCT [23] (46 women in the Netherlands) comparing sulprostone injection (500 micrograms im) versus placebo, and which found no significant difference between interventions in postpartum haemorrhage (defined as estimated blood loss greater than 500 mL; 5/22 [23%] with sulprostone *v* 10/24 [42%] with placebo; RR 0.55, 95% CI 0.22 to 1.35), severe postpartum haemorrhage (defined as estimated blood loss greater than 1000 mL; 1/22 [5%] with sulprostone *v* 2/24 [8%] with placebo; RR 0.36, 95% CI 0.04 to 3.24), and the need for further medical treatment (0/22 [0%] with sulprostone *v* 2/24 [8%] with placebo; RR 0.22, 95% CI 0.01 to 4.29). [16]

Sulprostone injection versus oxytocin:
We found one systematic review (search date 2007) [16] which identified one RCT comparing injectable sulprostone 500 micrograms versus oxytocin 5 IU in 51 low-risk women having vaginal delivery in the Netherlands. [23] It found no significant difference in measured blood loss between interventions (324 mL with prostaglandin E2 *v* 374 mL with oxytocin; significance assessment not performed). None of the women in either intervention group required additional medical treatment or manual removal of the placenta.

Sulprostone injection versus oxytocin plus ergometrine combinations:
We found one systematic review (search date 2007), [16] which identified one RCT. [24] The RCT (69 women with prior postpartum haemorrhage in the Netherlands) compared sulprostone (500 micrograms im) versus a fixed combination of oxytocin plus ergometrine. [24] It found trends of decreased blood loss and transfusion with sulprostone, but terminated the trial early when the manufacturer of the prostaglandin preparation issued a warning against intramuscular injection after receiving reports of cardiovascular complications outside the study.

Dinoprostone injection:
We found no RCTs.

Harms:

Sulprostone injection versus placebo:
The RCT identified by the review found no significant difference between sulprostone injection and placebo in “any adverse effect” (0/22 [0%] with sulprostone *v* 1/24 [4%] with placebo; RR 0.36, 95% CI 0.02 to 8.46), or nausea (0/22 [0%] with sulprostone *v* 1/24 [4%] with placebo; RR 0.36, 95% CI 0.02 to 8.46). It did not report data on vomiting, diarrhoea, headache, shivering, or fever. [23]

Sulprostone injection versus oxytocin:
The RCT [23] identified by the systematic review [16] comparing injectable sulprostone versus oxytocin gave no information on adverse effects, other than stating that no woman in either group had nausea.

Sulprostone injection versus oxytocin plus ergometrine combinations:
The RCT identified by the systematic review [16] gave no information on adverse effects. [24]

Dinoprostone injection:
We found no RCTs.

Comment:

Clinical guide:
Data on injectable prostaglandins are limited, but injectable sulprostone seems no better than oxytocin, ergot compounds, or combinations, and is associated with more adverse effects. Injectable prostaglandins are not available in many resource-poor countries.

OPTION MISOPROSTOL (SUBLINGUAL)

Morbidity
Compared with placebo/no intervention Misoprostol administered sublingually is more effective at reducing severe postpartum haemorrhage defined as blood loss of at least 1000 mL, but we don't know whether it is more effective at reducing placental retention (moderate-quality evidence).

Compared with oxytocin Sublingual misoprostol and oxytocin are equally effective at reducing postpartum haemorrhage defined as blood loss of 500 mL or of at least 1000 mL (moderate-quality evidence).

Compared with ergometrine Sublingual misoprostol and ergometrine are equally effective at reducing postpartum haemorrhage defined as blood loss of 500 mL or of at least 1000 mL, but ergometrine increases the risk of shivering (high-quality evidence).

Compared with oxytocin plus ergometrine combinations We don't know whether sublingual misoprostol is more effective at reducing blood loss, but it increases the risk of shivering and fever (low-quality evidence).

Need for further interventions
Compared with oxytocin Sublingual misoprostol and oxytocin are equally effective at reducing the need for additional oxytocics (moderate-quality evidence).

Compared with ergometrine Sublingual misoprostol and ergometrine are equally effective at reducing the need for manual removal of the placenta and the need for additional medical treatment (high-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits:

Sublingual misoprostol versus placebo/no intervention:
We found one systematic review [16] which identified one RCT (661 women delivering in local health centres in Guinea-Bissau) comparing misoprostol 600 micrograms sublingually versus placebo. It found no significant difference between groups in estimated blood of at least 500 mL, but found a significant decrease in blood loss of at least 1000 mL. There were no differences in retained placental tissue or need for transfer to hospital. There was a single death in the misoprostol group (see table 1, p 24).

Sublingual misoprostol versus oxytocin:
We found one systematic review (search date 2007) comparing sublingual misprostol versus all injected uterotonics. [16] The review identified two RCTs comparing sublingual misoprostil versus oxytocin. There was no meta-analysis for this particular comparison, therefore the RCTs were reported separately. Both RCTs identified by the review found no significant difference in mean blood loss, haemoglobin difference, or the use of additional oxytocics (see table 1, p 24). [25] [26]

Sublingual misoprostol versus ergometrine:
We found one systematic review (search date 2007) comparing sublingual misoprostol versus injectable uterotonics. [16] Two RCTs included in the review [27] [25] and one additional RCT [28] compared sublingual misprostol (50–400 micrograms) versus ergometrine. Both RCTs included in the review found no significant difference between groups for postpartum haemorrhage, severe postpartum heamorrhage, blood transfusion, or manual removal of placenta (see table 1, p 24). [16] The additional RCT (200 women at low risk for postpartum haemorrhage in India) compared misoprostol 400 micrograms sublingually versus methylergotomine 200 micrograms intramuscularly after delivery. [28] The RCT found no significant difference in mean total blood loss, mean haemoglobin, blood loss of at least 500 mL, change in haematocrit of at least 10%, or use of additional oxytocics (see table 1, p 24). [28]

Sublingual misoprostol versus oxytocin plus ergometrine combinations:
We found one systematic review (search date 2007) [16] comparing sublingual misoprostol versus all injectable uterotonics. The review included one RCT (60 women in Hong Kong) comparing

sublingual misoprostol 600 micrograms versus a fixed combination of oxytocin plus ergometrine 1 mL. [29] It found no difference in measures of blood loss or need for additional agents, although a significance assessment was not performed. One woman in the misoprostol group had a 4 L haemorrhage and required a hysterectomy (see table 1, p 24).

Harms:

Sublingual misoprostol versus placebo/no intervention:
The systematic review included one RCT that reported increased risk of shivering and fever (at least 38.0 °C), but no differences in nausea, vomiting, and diarrhoea (see table 1, p 24). [30] [16]

Sublingual misoprostol versus oxytocin:
The first RCT [25] included the systematic review [16] reported similar risks of vomiting and chills. The second RCT [26] included in the review found that, compared with oxytocin, misoprostol increased adverse effects, including fever, shivering, vomiting, headache, and metallic taste (see table 1, p 24).

Sublingual misoprostol versus ergometrine:
The RCTs in the systematic review [16] found that misoprostol significantly increased the risk of shivering compared with methylergometrine. They also found that, although the differences did not reach statistical significance, misoprostol increased the proportion of women with fever, nausea, vomiting, and headache compared with methylergometrine (see table 1, p 24). The additional RCT reported no significant difference in need for manual placenta removal, nausea, fever (at least 38.0 °C), and a significantly increased risk of shivering with misoprostol versus ergometrine (see table 1, p 24). [28]

Sublingual misoprostol versus oxytocin plus ergometrine combinations:
The single RCT identified by the systematic review [16] found significantly increased rates of shivering and fever with sublingual misoprostol compared with a fixed combination of oxytocin plus ergometrine (see table 1, p 24). [29]

Comment:

Clinical guide:
Misoprostol has been studied with great excitement because it is inexpensive, easily administered, and does not require strict refrigeration — making it potentially ideal for low-resource settings. Unlike other modes of administration, which have not been shown to be better than placebo/no intervention, a single RCT showed sublingual misoprostol to be more effective than placebo at preventing severe postpartum haemorrhage, but with significant adverse effects. It is unclear, given the many other studies that showed no effect compared with placebo, whether this reflects something unique about the mode of administration — for instance more rapid absorption — or a spurious result. Further studies of sublingual administration would be helpful. Given that it is, at best, equivalent to oxytocin and ergot compounds, and has a worse adverse-effect profile, oxytocin or an ergot compound is preferred when available. If misoprostol is used, current data support sublingual administration.

OPTION MISOPROSTOL (ORAL)

Morbidity
Compared with placebo/no intervention Oral misoprostol seems no more effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL or of at least 1000 mL, and seems to increase the rate of adverse effects, particularly fever and shivering (moderate-quality evidence).

Compared with ergot compounds Oral misoprostol and ergot compounds are equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL or of at least 1000 mL. However, oral misoprostol increases the risk of shivering and fever (high-quality evidence).

Compared with oxytocin Oral misoprostol and oxytocin seem equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL or of at least 1000 mL. However oral misoprostol is more likely to increase adverse effects, particularly fever, shivering, and diarrhoea (moderate-quality evidence).

Compared with oxytocin/ergometrine combinations We don't know whether misoprostol is more effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL or of at least 1000 mL. However, oral misoprostol increases the risk of shivering (moderate-quality evidence).

Need for further interventions
Compared with placebo/no intervention Oral misoprostol is no more effective at reducing the need for manual removal of the placenta or the need for additional medical treatment (high-quality evidence).

Compared with ergot compounds Oral misoprostol and ergot compounds are equally effective at reducing the need for manual removal of the placenta, the need for additional uterotonics, or the need for blood transfusion (high-quality evidence).

Compared with oxytocin Oral misoprostol and oxytocin seem equally effective at reducing the need for manual removal of the placenta, and for blood transfusions. However, oral misoprostol seems to reduce the need for additional uterotonics (moderate-quality evidence).

Compared with oxytocin/ergometrine combinations Oral misoprostol seems more effective at reducing the need for additional uterotonics, but we don't know whether it is more effective at reducing the need for manual removal of the placenta. However oral misoprostol and oxytocin/ergometrine combinations are equally effective at reducing the need for blood transfusion (moderate-quality evidence).

Mortality

Compared with placebo/no intervention Oral misoprostol is no more effective at reducing maternal mortality (high-quality evidence).

Compared with oxytocin Oral misoprostol and oxytocin seem equally effective at reducing mortality (high-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits:

Oral misoprostol versus placebo/no intervention:

We found one systematic review (search date 2007), which included a subgroup analysis comparing oral misoprostol versus placebo or no intervention (7 RCTs, 5153 women, with 2 RCTs using 400 micrograms and 6 RCTs using 600 micrograms of oral misoprostol [1 RCT had separate arms for each dose]). [16] Of the RCTs included in the review, three were performed in South Africa, one in Switzerland, one in France, and one in India. Three RCTs seem to be in low-risk populations, and risk status was not clearly specified in three RCTs. The seventh RCT included in the review was conducted in Gambia. It used oral ergometrine as a control group, which was considered "no intervention" as it is not thought to be effective. The systematic review reported significant qualitative and statistical heterogeneity for the outcome of severe postpartum hemorrhage (P value not reported), therefore data was reported for individual RCTs. Of the RCTs included in the review, three earlier RCTs found no significant difference in severe postpartum haemorrhage (at least 1000 mL) for oral misoprostol 600 micrograms versus placebo (see table 2, p 26). However, two more-recent RCTs included in the review found that misoprostol 600 micrograms significantly decreased the risk of severe postpartum haemorrahge (at least 1000 mL) (see table 2, p 26). Two RCTs included in the review found no significant difference in severe postpartum haemorrhage between 400 micrograms oral misoprostol and placebo. The RCTs included in the review found no significant difference in the use of additional uterotonics for 600 or 400 micrograms oral misoprostol versus placebo (see table 2, p 26). The review found that oral misoprostol significantly reduced the need for blood transfusion; however, there was no significant difference in maternal death or manual removal of the placenta (see table 2, p 26). [16]

Oral misoprostol versus ergot compounds:

We found one systematic review (search date 2007) comparing oral misoprostol versus any conventional injectable uterotonic (oxytocin, ergot compound, or combination of oxytocin and ergot compound). [16] The review identified 3 RCTs comparing oral misoprostol versus an ergot compound included in this review (ergometrine/methergine). The RCTs included in the review found no significant difference in severe postpartum haemorrhage (at least 1000 mL), postpartum haemorrhage (at least 500 mL), the use of additional uterotonics, blood loss, or manual removal of the placenta, between oral misoprostol compared with egot compounds (see table 3, p 28). [16]

Oral misoprostol versus oxytocin:

We found one systematic review (search date 2007) comparing oral misoprostol versus any conventional injectable uterotonic (oxytocin, ergot compound, or combination of oxytocin plus ergot compound). The review identified 11 RCTs comparing oral misoprostol 400–800 micrograms daily versus oxytocin (iv or im) in women having vaginal deliveries, and one RCT in women having caesarean delivery. [16] We found one additional RCT comparing oral misoprostol versus oxytocin that included women with cesearean delivery. [31] Most RCTs found no significant difference between oral misoprostol and oxytocin in maternal death, severe postpartum haemorrhage (at least 1000 mL), postpartum haemorrhage (at least 500 mL), blood transfusions, and manual removal of the placenta. There was some suggestion that oral misoprostol significantly reduced the need for use of additional uteronics (see table 4, p 29). The additional RCT (56 women undergoing caesarean delivery in Switzerland) compared oral misoprostol 800 micrograms versus oxytocin 20 IU. All women recieved an initial bolus of oxytocin 5 IU. It found no significant difference in calculated

blood loss. No women recieved blood transfusions or additional uterotonic agents (see table 4, p 29). [31]

Oral misoprostol versus oxytocin plus ergot compounds:
We found one systematic review (search date 2007) comparing oral misoprostol versus any conventional injectable uterotonic (oxytocin, ergot compound, or combination of oxytocin and ergot compound). [16] The review identified three RCTs comparing oral misoprostol (400–600 micrograms/day) versus oxytocin plus ergometrine (oxytocin 5 IU plus 0.5 mg ergometrine or oxytocin 10 IU plus 1 mL methylergometrine). We also found one additional RCT. [32] Most of the RCTs included in the review and the additional RCT found no significant difference in severe postpartum haemorrhage (at least 1000 mL), postpartum haemorrhage (at least 500 mL), blood transfusions, and manual removal of the placenta between oral misoprostol versus oxytocin plus ergometrine. However the evidence suggests that oral misoprostol significantly increased the risk of the use of additional uterotonics (see table 5, p 33). [16] [32]

Harms:

Oral misoprostol versus placebo/no intervention:
The systematic review found that, compared with placebo, oral misoprostol significantly increased adverse effects, particularly shivering and fever. Significant heterogeneity was noted for nausea, vomiting, and abdominal pain, with some studies showing increased and others decreased risk. The review found no significant differences between groups for risk of headache or diarrhoea. [16] Notably, some of the heterogeneity may have resulted from the inclusion of the Gambia study, which used oral ergotrate as the comparison arm. Although useful as an efficacy comparison, as it is thought to not have effect in preventing postpartum hemorrhage, it is likely to have noticeable adverse effects (see table 2, p 26).

Oral misoprostol versus ergot compounds:
The RCT included in the review reported no significant differences in nausea, vomiting, or diarrhoea between oral misoprostol versus ergot compounds. However the RCTs reported that oral misoprostol singificantly increased the risk of shivering and fever compared with ergot compounds (see table 3, p 28). [16]

Oral misoprostol versus oxytocin:
Most of the RCTs included in the review reported no significant difference in nausea, vomiting, or diarrhoea between oral misoprostol versus oxytocin. Most of the RCTs included in the review found that oral misoprostol 600 micrograms significantly increased the risk of shivering compared with oxytocin. The results for fever were inconclusive (see table 4, p 29). [16] The additional RCT also reported an increased risk of shivering for oral misoprostol 800 micrograms compared with oxytocin (see table 5, p 29). [31]

Oral misoprostol versus oxytocin plus ergometrine combinations:
The RCTs included in the review and the additional RCT reported no signficant difference between oral misoprostol versus oxytocin plus ergometrine in nausea, vomiting, diarrhoea, and headache. [16] [32] However, the review and the additional RCT found that oral misoprostol significantly increased the risk of shivering compared with oxytocin plus ergometrine. [16] [32] The results for fever were conflicting (see table 5, p 33). [16] [32]

Comment:

Clinical guide:
Misoprostol has been studied with great excitement because it is inexpensive, easily administered, and does not require strict refrigeration (must be kept at less than 26 °C), potentially making it ideal for low-resource settings. Unfortunately, although oral misoprostol seemed similar to the other interventions included here, it may be no more effective than placebo, and with significant adverse effects. Oral misoprostol is not registered for these obstetric uses and is generally unavailable in Africa and many other countries.

OPTION MISOPROSTOL (RECTAL)

Morbidity
Compared with placebo/no intervention Rectal misoprostol is no more effective at reducing severe postpartum haemorrhage defined as blood loss of at least 1000 mL (high-quality evidence).

Compared with oxytocin Rectal misoprostol and oxytocin are equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL or of at least 1000 mL (high-quality evidence).

Compared with oxytocin plus ergometrine combinations We don't know whether rectal misoprostol is more effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL, but it is more effective at reducing severe postpartum haemorrhage defined as blood loss of at least 1000 mL (moderate-quality evidence).

Compared with carboprost injection Rectal misoprostol and carboprost injection are equally effective at reducing postpartum haemorrhage defined as blood loss of at least 500 mL. However, rectal misoprost is associated with more adverse effects, such as nausea, vomiting, diarrhoea, and shivering (moderate-quality evidence).

Need for further interventions
Compared with placebo/no intervention Rectal misoprostol is no more effective at reducing the need for additional medical treatment (high-quality evidence).

Compared with oxytocin Rectal misoprostol and oxytocin are equally effective at reducing the need for blood transfusion, but we don't know whether rectal misoprostol is more effective at reducing the need for additional uterotonics (moderate-quality evidence).

Compared with oxytocin plus ergometrine combinations Misoprostol increases the need for additional uterotonics (high-quality evidence).

Compared with carboprost injection Rectal misoprostol increases the need for additional oxytocics (high-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table , p 36 .

Benefits:

Rectal misoprostol versus placebo/no intervention:
We found one systematic review (search date 2007) comparing prostaglandin analogues versus placebo/no intervention, which included a subgroup analyses for rectal misoprostol (1 RCT). [16] The RCT identified by the review (550 low-risk women in South Africa) found no significant difference between rectal misoprostol 400 micrograms and placebo in severe postpartum haemorrhage and the need for additional medical treatment. One woman in the rectal misoprostol group required manual placenta removal (see table 6, p 34).

Rectal misoprostol versus oxytocin:
We found one systematic review (search date 2007) comparing rectal misoprostol versus any conventional injectable uterotonic (oxytocin, ergot compound, or combination of oxytocin and ergot compound). [16] Four RCTs identified by the review compared rectal misoprostol 400 micrograms versus oxytocin (10–20 IU). The RCTs included in the review found no significant difference in maternal death, severe postpartum haemorrhage (at least 1000 mL), postpartum haemorrhage (at least 500 mL), manual removal of the placenta, and blood transfusions between rectal misoprostol and oxytocin. Results for the use of additional uterotonics were conflicting (see table 6, p 34). [16]

Rectal misoprostol versus oxytocin plus ergometrine combinations:
We found one systematic review (search date 2007) comparing rectal misoprostol versus any conventional injectable uterotonic (oxytocin, ergot compound, or combination of oxytocin and ergot compound). [16] The review identified two RCTs comparing rectal misoprostol versus syntometrine. The RCTs included in the review found conflicting results for postpartum haemorrhage (at least 500 mL), but found that rectal misoprostol significantly increased the risk of severe postpartum haemorrhage (at least 1000 mL) and the need for additional uterotonic agents (see table 6, p 34). [16]

Rectal misoprostol versus carboprost injection:
We found one systematic review (search date 2007) which identified one RCT. The RCT (120 full-term, low-risk women in rural India) compared rectal misoprostol 400 micrograms versus 15-methyl prostaglandin F2-alpha 125 micrograms. It found no significant difference between groups for postpartum haemorrhage (at least 500 mL), but found that misoprostol significantly increased the need for additional oxytocics. One woman in the misoprostol group, and none in the prostaglandin F2-alpha group required blood transfusion. No women required manual placenta removal or had severe postpartum haemorrhage (at least 1000 mL) (see table 6, p 34). [16]

Harms:

Rectal misoprostol versus placebo/no intervention:
The RCT comparing rectal misoprostol versus placebo found no significant difference between interventions in vomiting (1/271 [0.4%] with misoprostol *v* 1/275 [0.4%] with placebo; RR 1.01, 95% CI 0.06 to 16.14), shivering (1/34 [3%] with misoprostol *v* 4/36 [11%] with placebo; RR 0.26, 95% CI 0.03 to 2.25), or abdominal pain (1/271 [0.4%] with misoprostol *v* 0/275 [0%] with placebo; RR 3.04, 95% CI 0.12 to 74.40). The RCT did not report data on nausea, diarrhoea, headache, or fever.

Rectal misoprostol versus oxytocin:
The RCTs included the systematic review reported no significant difference in nausea, vomiting, abdominal pain, and diarrheoa between rectal misoprostol and oxytocin. However most of the

RCTS included in the review reported that rectal misoprostol significantly increased shivering and fever compared with oxytocin (see table 6, p 34). [16]

Rectal misoprostol versus oxytocin plus ergometrine combinations:
The second RCT included in the review reported that rectal misoprostol significantly increased the risk of shivering and fever, but found no significant difference in vomiting and diarrhoea compared with ergometrine combinations (see table 6, p 34). [16]

Rectal misoprostol versus carboprost injection:
The RCT included in the review noted significantly more gastrointestinal adverse effects, such as nausea, vomiting, and diarrhoea, in the 15-methyl prostaglandin F2-alpha group. Five women in the misoprostol group and none in the injected prostaglandin group reported shivering (see table 6, p 34). [16]

Comment: **Clinical guide:**
Misoprostol has been studied with great excitement because it is inexpensive, easily administered, and does not require strict refrigeration, potentially making it ideal for low-resource settings. Unfortunately, rectally administered misoprostol is less effective than other interventions, and seems no more effective than placebo, and with significant adverse effects.

OPTION MISOPROSTOL (VAGINAL)

Morbidity
Compared with placebo/no intervention We don't know whether vaginal misoprostol is more effective at reducing blood loss (very low-quality evidence).

For GRADE evaluation of interventions for postpartum haemorrhage, see table, p 36 .

Benefits: **Vaginal misoprostol versus placebo/no intervention:**
One RCT (100 women delivering after 32 weeks' gestation) compared misoprostol 400 micrograms administered vaginally versus placebo. It found no significant difference in estimated blood loss (206 mL with vaginal misoprostol*v* 171 mL with placebo), haemoglobin at 24 hours postpartum (11.1 g/dL *v* 11.6 g/dL), or change in haemoglobin (1 g/dL *v* 1 g/dL). The study was a three-way comparison of rectal and vaginal misoprostol with placebo, and separate statistical comparisons were not performed. [33]

Harms: **Vaginal misoprostol versus placebo/no intervention:**
In the single RCT, “side-effects were not asked about directly, but none were reported”. [33]

Comment: **Clinical guide:**
Misoprostol has been studied with great excitement because it is inexpensive, easily administered, and does not require strict refrigeration, potentially making it ideal for low-resource settings. Limited evidence is available regarding vaginally administered misoprostol. The single available study showed no difference from placebo.

GLOSSARY

Active management Management of the third stage of labour through a combination of interventions, usually including: immediate cord clamping, cutting, and drainage; controlled cord traction; and use of an oxytocic agent (oxytocin, a fixed combination of oxytocin plus ergometrine, ergot compound, etc.).
Controlled cord traction involves applying traction to the umbilical cord after the uterus has begun to contract. This can be done constantly or intermittently, usually every few minutes.
Ergot compounds Naturally occurring alkaloids that cause uterine contraction. Available for clinical use as ergometrine, methylergonovine, and methergine.
Expectant management Management of the third stage by passive means. No active interventions such as oxytocic administration or cord traction are used. In general, the placenta is allowed to be delivered by a combination of gravity and natural uterine contractions, sometimes in conjunction with nipple stimulation.
Immediate cord drainage Allowing the blood in the placenta to drain from the cut end of the umbilical cord immediately after the cord is clamped and cut.
Manual placenta removal Removal of the placenta by a hand placed through the vagina into the uterus. It is usually performed for retained placental tissue or with postpartum haemorrhage occurring before delivery of the placenta.
Oxytocic agent Any agent that makes the uterus contract.
Oxytocin Peptide hormone endogenously synthesised in the hypothalamus (supraoptic and paraventricular nuclei) and released from the posterior pituitary, and important for uterine contractility. Given either intramuscularly or intravenously for the induction or augmentation of labour, and the prevention or treatment of postpartum haemorrhage.
Retained placental tissue Placenta that has not been delivered within a specified length of time, often 30 minutes, from time of the delivery of the baby.

Uterine massage involves manually rubbing the uterine fundus through the abdominal wall immediately after birth.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Sheehan's syndrome is caused by necrosis of the pituitary gland with associated hypopituitarism, resulting from severe postpartum haemorrhage. Although it can cause hypotension and shock immediately postpartum, in most cases the onset is slower – days, weeks, or even years later. Common features are lack of lactation postpartum, amenorrhoea, loss of pubic hair, weight loss, and lethargy. Although increasingly rare in the western world, it is one of the most common causes of hypopituitarism in resource-poor countries.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Carboprost injection One systematic review [16] and one additional RCT added [19] comparing carboprost versus methylergometrine. The systematic review included two RCTs and reported them separately. The first RCT included in the review reported no instances of postpartum haemorrhage for either intervention. The second RCT included in the review reported that carboprost decreased blood loss in the third and fourth stages of labour, but found no significant difference for postpartum haemorrhage compared with methylergometrine. [16] The additional RCT found no significant difference for postpartum haemorrhage or blood loss for carboprost compared with methylergometrine, but found that methylergometrine reduced duration of third stage labour compared with carboprost. [19] Categorisation unchanged (Trade-off between benefits and harms).
Controlled cord traction One systematic review added comparing controlled cord traction alone versus minimal intervention in third stage labour. [5] The review included two quasi-randomised trials with conflicting results, no conclusions were reported due to serious methodological flaws of the original data. Categorisation unchanged (Likely to be beneficial).
Ergot compounds One systematic review added comparing ergot compounds versus placebo/no treatment. [22] The review found that ergot compounds decrease the risk of postpartum haemorrhage, mean blood loss, and additional uterotonic administration, but found no significant difference in the risk of retained placenta or blood transfusion compared with placebo or no treatment. The review also reported that ergot administration increased the risk of vomiting, elevated blood pressure, and pain after birth requiring pain medication. Categorisation unchanged (Trade-off between benefits and harms).
Misoprostol (oral) One systematic review and two additional RCTs added comparing oral misoprostol versus placebo/no intervention, or ergot compounds, or oxytocin, or oxytocin plus ergot compounds. [16] [32] [31] Most of the new evidence found no significant difference between oral misoprostol versus any of the comparison groups for maternal death, severe postpartum haemorrhage (at least 1000 mL), postpartum haemorrhage (at least 500 mL), use of additional uterotonics, blood transfusions, and a manual removal of the placenta. The new evidence also reported that oral misoprostol increased the risk of some adverse effects including, nausea, vomiting, shivering, fever, headache, and diarrhoea. Categorisation unchanged (Likely to be ineffective or harmful).
Misoprostol (rectal) One systematic review added comparing rectal misoprostol versus oxytocin, oxytocin plus ergometrine, or carboprost injections. [16] The review found no differences between rectal misoprostol versus oxytocin for maternal death, severe postpartum haemorrhage (at least 1000 mL), postpartum haemorrhage (at least 500 mL), manual removal of the placenta, or blood transfusions. One of the RCTs included in the review found that rectal misoprostol increased the use of additional uterotonics versus oxytocin. No differences were found for rectal misoprostol versus oxytocin plus ergometrine for postpartum haemorrhage (at least 500 mL), but the review found that rectal misoprostol increased the risk of severe postpartum haemorrhage (at least 1000 mL), the use of additional uterotonics, and blood transfusions, compared with oxytocin plus ergometrine. The review found no differences between rectal misoprostol versus carboprost injection for postpartum haemorrhage (at least 500 mL), but found that rectal misoprostol increased the use of additional uterotonics. The review also reported that rectal misoprostol increased the risk of shivering and fever. [16] Categoristion unchanged (Likely to be ineffective or harmful).
Misoprostol (sublingual) One systematic review added comparing sublingual misoprostol versus oxytocin or ergotomine. [16] The systematic review found no significant difference between sublingual misoprostol and oxytocin for blood loss of at least 500 mL or blood loss of at least 1000 mL. The review reported no significant difference between sublingual misoprostol versus methylergonovine for blood loss of at least 500 mL or blood loss of at least 1000 mL, the review also found no significant difference in mean total blood loss for sublingual misoprostol versus methylergotomine. Categorisation unchanged (Unknown effectiveness).
Oxytocin One RCT added comparing oxytocin (5 IU at time of delivery) versus no oxytocin. [12] All women received immediate cord clamping and controlled cord traction. The RCT found that: postpartum anaemia was less frequent among women administered oxytocin; that oxytocin improved haemoglobin drop; and that the third stage labour was shorter with oxytocin than with no oxytocin. Categorisation unchanged (Beneficial).
Uterine massage One RCT added comparing unterine massage plus active managment versus active managment alone. [10] It found that uterine massage reduced blood loss at 30 and 60 minutes post delivery, and reduced the need for additional uterotonic agent compared with active management. However there was no signficant difference between groups in rates of postpartum haemorrhage. Categorisation changed from Unknown effectiveness to Likely to be beneficial (based on consensus).

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Disclaimer

TABLE 1 **Sublingual misoprostol versus placebo/oxytocin/ergometrine/oxytocin plus ergometrine**

Study	Population/ Intervention	Results	Adverse Effects
Systematic review [16] one RCT [30]	661 women delivering in local health centres in Guinea-Bissau: sublingual misoprostol (600 micrograms) versus placebo.	**Maternal death:** 1 death in the misoprostol group **Estimated blood loss (at least 500 mL):** 45% with misoprostol *v* 51% with placebo; RR 0.89, 95% CI 0.76 to 1.04 **Blood loss (at least 1000 mL):** 11% with misoprostol *v* 17% with placebo; RR 0.66, 95% CI 0.45 to 0.98 **Estimated blood loss (at least 500 mL):** 2% with misoprostol *v* 8% with placebo; RR 0.28, 95% CI 0.12 to 0.64 **Retained placental tissue:** 3% in each group Transfer to hospital: 0.9% in each group.	**Shivering:** 57% misoprostol *v* 24% placebo; RR 2.43, 95% CI 1.96 to 3.02 **Fever (at least 38.0 °C):** 24% with misoprostol *v* 3% with placebo; RR 7.09, 95% CI 3.84 to 13.1 **Nausea:** 1% with misoprostol *v* 1% with placebo; RR 0.50, 95% CI 0.09 to 2.72 **Vomiting:** 3% with misoprostol *v* 1% with placebo; RR 2.51, 95% CI 0.79 to 7.91 **Diarrhoea:** 3% with misoprostol *v* 1% with placebo; RR 2.50, 95% CI 0.79 to 7.8
Systematic review [16] one RCT [25]	50 women in Columbia: sublingual misoprostol (50 micrograms) versus oxytocin (16 mIU/minute) after cord clamping	**Mean blood loss:** 389.4 mL with misoprostol *v* 467.4 mL with oxytocin, mean difference –78 mL, 95% CI –281.7 mL to +125.7 mL **Blood loss (at least 500 mL):** 7/25 (28%) with misoprostol *v* 8/25 (32%) with oxytocin, RR 0.88, 95% CI 0.37 to 2.5 **Blood loss at least 1000 mL):**1/25 (4%) with misoprostol *v* 3/25 (12%) with oxytocin, RR 0.33, 95% CI 0.04 to 2.99)	**Vomiting**: 0/25 (0%) with misoprostol v 1/25 (4%) with oxytocin, no significance assessment performed **Chills**: 1/25 (4%) with misoprostol *v* 0/25 (0%) with oxytocin, no significance assessment performed
Systematic review [16] one RCT [26]	100 women undergoing elective or emergency caesarean delivery in India: sublingual misoprostol (400 micrograms) versus oxytocin (20 IU iv) after delivery	**Estimated blood loss:** 819 mL with misoprostol v 974 mL with oxytocin, mean difference –155 mL, 95% CI –258.9 mL to –51.6 mL **Blood loss at least 500 mL):** 47/50 (94%) with misoprostol *v* 46/50 (92%) with oxytocin, RR 1.02, 95% CI 0.92 to 1.14 **Blood loss (at least 1000 mL):** 6/50 (12%) with misoprostol *v* 10/50 (20%) with oxytocin, RR 0.60, 95% CI 0.24 to 1.53 **Haemoglobin difference:** (0.4 mL with misoprostol *v* 0.6 mL with oxytocin, mean difference –0.2 mL, 95% CI –0.88 to +0.48 mL **Use of additional oxytocics**: 16/50 (32%) with misoprostol *v* 18/50 (36%) with oxytocin, RR 0.89, 95% CI 0.51 to 1.54	**Fever:** 8/50 (16%) with misoprostol *v* 2/50 (4%) with methylergotamine, RR 4.0, 95% CI 0.89 to 17.91 **Shivering:** 13/50 (26%) with misoprostol *v* 2/50 (4%) with methylergotomine, RR 6.5, 95% CI 1.6 to 27.3 **Vomiting:** 8/50 (16%) with misoprostol *v* 6/50 (12%) with methylergotomine, RR 1.33, 95% CI 0.50 to 3.56) **Headache**: 6/50 (12%)with misoprostol *v* 8/50 (16%) with methylergotomine, RR 0.75, 95% CI 0.28 to 2.00 **Metallic taste**: 7/50 (14%) with misoprostol *v* 0/50 (0%) with methylergotomine, P = 0.01
Systematic review [16] one RCT [27]	120 low-risk women in India: sublingual misoprostol (400 micrograms) versus methylergometrine (200 micrograms im)	**Postpartum haemorrhage (at least 500 mL):** 2/60 (3%) with misoprostol *v* 0/60 (0%) with methylergometrine; P = 0.50 **Severe postpartum haemorrhage (at least 1000 mL):** 0 women with either intervention **Blood transfusion**: 0 women with either intervention **Further medical treatment:** 5/60 (8%) with misoprostol *v* 3/60 (5%) with methylergometrine; P = 0.71 **Manual placenta removal:** 0/60 (0%) with misoprostol *v* 1/60 (2%) with methylergometrine; P = 1.0	**Shivering:** 22% with misoprostol *v* 0% with methylergometrine; P = 0.0001 **Fever:** 7% with misoprostol *v* 0% with methylergometrine; P = 0.057 **Nausea:** 13% with misoprostol *v* 7% with methylergometrine; RR 2.00, 95% CI 0.64 to 6.29 **Vomiting**: 7% with misoprostol *v* 3% with methylergometrine; RR 2.00, 95% CI 0.38 to 10.51 **Headache:** 7% misoprostol *v* 5% with methylergometrine; RR 1.33, 95% CI 0.31 to 5.70
Systematic review [16] one RCT [25]	50 women in Columbia: sublingual misoprostol (50 micrograms) versus methylergonovine (0.2 mg im)	**Blood loss:** 389.4 mL with misoprostol *v* 546.8 mL methylergonovine, mean difference –157 mL, 95% CI –331.9 to +17.1 mL **Blood loss (at least 500 mL):** 7/25 (28%) with misoprostol *v* 12/25 (48%) methylergonovine, RR 0.58, 95% CI 0.28 to 1.3 **Blood loss (at least 1000 mL):** 4% with misoprostol *v* 12% with methylergonovine, RR 0.33, 95% CI 0.04 to 2.99	**Chills:** One person in each group

Study	Population/ Intervention	Results	Adverse Effects
[28]	200 women at low risk for postpartum hemorrhage in India: sublingual misoprostol (400 micrograms) versus methylergotomine (200 micrograms im) delivery	**Mean total blood loss:** 137.6 mL with misoprostol *v* 125.79 mL with methylergometrine, P = 0.25 **Mean haemoglobin:** 0.31 g/dL with misoprostol *v* 0.25 g/dL with methylergotomine, P = 0.12 **Blood loss (at least 500 mL):** 1/100 (1%) with misoprostol *v* 0/100 (0%) with methylergotomine, P = 1.0 **Change in haematocrit at least 10%:** 2/100 (2%) with misoprostol *v* 1/100 (1%) with methylergotomine, P = 1.0 **Use of additional oxytocics:** 4/100 (4%) with misoprostol *v* 2/100 (2%) with methylergotomine, P = 0.68 **Manual placenta removal:** 0/100 (0%) with misoprostol *v* 1/100 (1%) with methylergometrine, P = 1.0	**Nausea:** 4/100 (4%) with misoprostol *v* 2/100 (2%) with methylergometrine, P = 0.68 **Fever (at least 38.0 °C):** 6/100 (6%) with misoprostol *v* 1/100 (1%) with methylergometrine, P = 0.11 **Shivering**: 18/100 (18%) with misoprostol *v* 4/100 (4%) with methylergometrine, P = 0.003
Systematic review [16] one RCT [29]	60 women in Hong Kong: sublingual misoprostol (600 micrograms) versus a fixed combination of oxytocin plus ergometrine 1 ml	**Blood loss**: 187 mL with misoprostol *v* 183 mL with oxytocin plus ergometrine: mean difference +40 mL, 95% CI –10.73 mL to +18.73 mL **Hysterectomy:** One woman in the misoprostol group had a 4 L haemorrhage and required a hysterectomy	**Shivering and fever:** 33% with misoprostol *v* 0% with oxytocin plus ergometrine; P = 0.001

TABLE 2 **Oral misoprostol versus placebo/no intervention**

Study	Population/ Intervention	Results	Adverse Effects
[16]	oral misoprostol (400 or 600 micrograms) *v* placebo/no intervention	**Maternal death:** 2 RCTs, 2/1442 (0.13%) with misoprostol *v* 1/1407 (0.07%) with placebo, RR 1.16, 95% CI 0.24 to 8.81 **Blood transfusion (600 micrograms):** 3 RCTs, 2/1311 (0.1%) with misoprostol *v* 10/1038 (0.9%) with placebo, RR 0.24, 95% CI 0.06 to 0.94 **Blood transfusion (400 micrograms):** 2 RCTs, 3/1761 (0.3%) with misoprostol *v* 12/1758 (0.6%) with placebo **Manual removal of placenta (600 micrograms)**: 2 RCTs, 4/500 (0.8%) with misoprostol *v* 3/500 (0.6%) with placebo, RR 1.33, 95% CI 0.30 to 5.93 **Manual removal of placenta (400 micrograms):** 2 RCTs, 1/450 (0.2%) with misoprostol *v* 3/450 (0.6%) with placebo, RR 0.43, 95% CI 0.06 to 2.89	**Any adverse effect:** 1 RCT, 54/250 (22%) with misoprostol *v* 26/250 (10%) with placebo, RR 2.08, 95% CI 1.35 to 3.20 **Headache (600 micrograms):** 2 RCTs, 5/499 (1.0%) with misoprostol *v* 2/499 (0.4%) with placebo, RR 2.20, 95 % CI 0.50 to 9.77 **Headache (400 micrograms):** 1 RCT, 2/199 (1%) with misoprostol *v* 0/199 (0%) with placebo, RR 5.00, 95% CI 0.24 to 103.49 **Diarrhoea:** 3 RCTs, 7/1129 (0.6%) with misoprostol *v* 7/1098 (0.6%) with placebo, RR 0.96, 95% CI 0.34 to 2.72 **Fever (at least 38 °C):** 207/1697 (12%) with misoprostol *v* 32/1727 (2%) with placebo, RR 6.40, 95% CI 4.47 to 9.18
RCTs included in the systematic review [16]			
France 2001	602 women with vaginal delivery: oral misoprostol (600 micrograms) *v* no uterotonic	**Severe postpartum haemorrhage (at least 1000 mL):** 16/186 (7%) with misoprostol *v* 13/220 (6%) with placebo, RR 1.46, 95% CI 0.72 to 2.95 **Postpartum haemorrhage (at least 500 mL):** 52/186 (28%) with misoprostol *v* 60/220 (27%) with placebo, RR 1.03, 95% CI 0.75 to 1.41	**Vomiting:** 7/186 (4.0%) with misoprostol *v* 1/220 (0.4%) with placebo, RR 8.28, 95% CI 1.03 to 66.68 **Shivering:** 5/186 (3%) with misoprostol *v* 0/220 (0%) with placebo, RR 13.00, 95% CI 0.72 to 233.56
Gambia 2005	1229 women with vaginal delivery: oral misoprostol (600 micrograms) *v* no intervention (ergometrine)	**Severe postpartum haemorrhage (at least 1000 mL):** 2/629 (0.3%) with misoprostol *v* 4/599 (0.6%) with placebo, RR 0.48, 95% CI 0.09 to 2.59 **Postpartum haemorrhage (at least 500 mL):** 69/629 (11%) with misoprostol *v* 75/599 (13%) with placebo, RR 0.91, 95% CI 0.67 to 1.25 **Blood loss:** 281 mL with misoprostol *v* 292 mL with placebo, WMD –11.00, 95% CI –30.75 to +8.75	**Nausea**: 6/630 (1%) with misoprostol *v* 14/599 (2%) with placebo, RR 0.41, 95% CI 0.16 to 1.05 **Vomiting:** 18/630 (3%) with misoprostol *v* 34/599 (6%) with placebo, RR 0.50, 95% CI 0.29 to 0.88 **Shivering:** 202/630 (32%) with misoprostol *v* 70/599 (12%) with placebo, RR 2.74, 95% CI 2.14 to 3.52
India 2006	1620 women with vaginal delivery: oral misoprostol (600 micrograms) *v* placebo	**Severe postpartum haemorrhage (at least 1000 mL):** 2/812 (0.2%) with misoprostol *v* 10/808 (1.2%) with placebo, RR 0.20, 95% CI 0.04 to 0.91 **Postpartum haemorrhage (at least 500 mL):** 52/812 (6%) with misoprostol *v* 97/808 (12%) with placebo, RR 0.53, 95% CI 0.39 to 0.74 **Blood loss:** 214.00 mL with misoprostol *v* 262.30 mL with placebo, WMD –48.00, 95% CI –65.19 to –30.81 **Additional uterotonics:** 3/812 (0.3%) with misoprostol *v* 6/808 (0.7%) with placebo, RR 0.50, 95% CI 0.12 to 1.98	**Shivering**: 424/812 (52%) with misoprostol *v* 140/808 (17%) with placebo, RR 3.01, 95% CI 2.56 to 3.55

Study	Population/ Intervention	Results	Adverse Effects
South Africa 1998a	600 women: oral misoprostol (400 or 600 micrograms) *v* placebo	**Oral misoprostol (600 micrograms)** **Severe postpartum haemorrhage (at least 1000 mL):** 17/200 (9%) with misoprostol *v* 6/200 (3%) with placebo, RR 2.83, 95% CI 1.14 to 7.04 **Additional uterotonics:** 32/200 (16%) with misoprostol *v* 23/200 (12%) with placebo, RR 1.39, 95% CI 0.85 to 2.29 **Severe postpartum haemorrhage (at least 1000 mL):** 16/200 (8%) with misoprostol *v* 6/200 (3%) with placebo, RR 2.67, 95% CI 1.07 to 6.68 **Additional uterotonics:** 28/200 (14%) with misoprostol *v* 23/200 (12%) with placebo, RR 1.22, 95% CI 0.73 to 2.04	**Oral misoprostol (600 micrograms)** **Nausea:** 1/199 (0.5%) with misoprostol *v* 0/199 (0%) with placebo, RR 3.00, 95% CI 0.12 to 73.20 **Vomiting:** 1/199 (0.5%) with misoprostol *v* 1/199 (0%) with placebo, RR 1.00, 95% CI 0.06 to 15.88 **Abdominal pain**: 12/199 (6%) with misoprostol *v* 2/199 (1%) with placebo, RR 6.00, 95% CI 1.36 to 26.46 **Shivering**: 81/199 (41%) with misoprostol *v* 30/199 (15%) with placebo, RR 2.70, 95% CI 1.87 to 3.91 **Oral misoprostol (400 micrograms)** **Nausea:** 1/199 (0.5%) with misoprostol *v* 0/199 (0%) with placebo, RR 3.00, 95% CI 0.12 to 73.20 **Vomiting:** 1/199 (0.5%) with misoprostol *v* 1/199 (0%) with placebo, RR 1.00, 95% CI 0.06 to 15.88 **Abdominal pain:** 8/199 (4%) with misoprostol *v* 2/199 (1%) with placebo, RR 4.00, 95% 0.86 to 18.60 **Shivering:** 65/199 (32%) with misoprostol *v* 30/199 (15%) with placebo, RR 2.17, 95% CI 1.47 to 3.19
South Africa 2001	600 women: oral misoprostol (600 micrograms) *v* placebo	**Severe postpartum haemorrhage (at least 1000 mL):** 27/300 (9%) with misoprostol *v* 29/299 (10%) with placebo, RR 0.93, 95% CI 0.56 to 1.53 **Additional uterotonics:** 42/300 (14%) with misoprostol *v* 54/300 (18%) with placebo, RR 0.78, 95% CI 0.54 to 1.13	**Nausea:** 5/300 (2%) with misoprostol *v* 1/300 (0.3%) with placebo, RR 5.00, 95% CI 0.59 to 42.54 **Vomiting:** 4/300 (1%) with misoprostol *v* 2/300 (0.6%), RR 2.00, 95% CI 0.37 to 10.84 **Abdominal pain:** 47/300 (16%) with misoprostol *v* 31/300 (10%) with placebo, RR 1.52, 95% CI 0.99 to 2.32 **Shivering:** 133/300 (44%) with misoprostol *v* 33/300 (11%) with placebo, RR 4.03, 95% CI 2.85 to 5.70
South Africa 1998b	500 women: oral misoprostol (400 micrograms) *v* placebo	**Severe postpartum haemorrhage (at least 1000 mL):** 15/250 (6%) with misoprostol *v* 23/250 (9%) with placebo, RR 0.65, 95% CI 0.35 to 1.22 **Additional uterotonics:** 21/250 (8%) with misoprostol *v* 33/250 (13%) with placebo, RR 0.64, 95% CI 0.38 to 1.07	**Abdominal pain:** 2/250 (1%) with misoprostol *v* 7/250 (3%) with placebo, RR 0.29, 95% CI 0.29. 95% CI 0.06 to 1.36 **Shivering:** 48/250 (19%) with misoprostol *v* 13/250 (5%) with placebo, RR 3.69, 95% CI 2.05 to 6.64
Switzerland 1999	65 women with vaginal delivery: oral misoprostol (600 micrograms) *v* placebo	**Postpartum haemorrhage (at least 500 mL):** 2/31 (6%) with misoprostol *v* 5/34 (15%) with placebo, RR 0.44, 95% CI 0.09 to 2.10 **Blood loss:** 345. mL with misoprostol *v* 417. mL with placebo, RR –72.00, 95% CI –122.9 to –21.10 **Additional uterotonics:** 5/31 (16%) with misoprostol *v* 13/34 (38%) with placebo, RR 0.42, 95% CI 0.17 to 1.05	**Shivering:** 7/31 (23%) with misoprostol *v* 1/34 (3%) with placebo, RR 7.68, 95% CI 1.00 to 58.92

TABLE 3 **Oral misoprostol *v* ergot compounds**

Study	Population/ Intervention	Results	Adverse Effects
[16] 1 RCT	213 women with vaginal delivery in Belgium: oral misoprostol (600 micrograms) versus methylergometrine (200 micrograms)	**Severe postpartum haemorrhage (at least 1000 mL):** 1/100 (1%) with misoprostol *v* 0/100 (0%) with methylergometrine, RR 3.00, 95% CI 0.12 to 72.77 **Postpartum haemorrhage (at least 500 mL):** 8/96 (8%) with misoprostol *v* 4/93 (4%) with methylergometrine, RR 1.94, 95% CI 0.60 to 6.22 **Additional uterotonics**: 12/94 (13%) with misoprostol *v* 4/91 (4%) with methylergometrine, RR 2.90, 95% CI 0.97 to 8.67 **Blood transfusion:** 1/100 (1%) with misoprostol *v* 1/100 (1%) with methylergometrine, RR 1.00, 95% CI 0.06, 15.77 **Manual placenta removal:** 4/100 (4%) with misoprostol *v* 3/100 (3%) with methylergometrine, RR 1.33, 95% CI 0.31 o 5.81	**Nausea:** 20/87 (23%) with misoprostol *v* 30/94 (32%) with methylergometrine, RR 0.72, 95% CI 0.44 to 1.17 **Vomiting:** 13/87 (15%) with misoprostol *v* 18/94 (19%) with methylergometrine, RR 0.78, 95% CI 0.41 to 1.50 **Shivering:** 66/86 (77%) with misoprostol *v* 38/94 (40%) with methylergometrine, RR 1.90, 95% CI 1.45 to 2.49 **Fever (at least 38 °C):** 34/100 (34%) with misoprostol *v* 3/100 (3%) with methylergometrine, RR 11.33, 95% CI 3.60 to 35.70
[16] 1 RCT	200 women with singleton deliveries in India: oral misoprostol (600 micrograms) immediately after delivery versus methylergometrine (0.2 mg iv) at delivery of anterior shoulder	**Postpartum haemorrhage (at least 500 mL):** 8/100 (8%) with misoprostol *v* 6/100 (6%) with methylergometrine, RR 1.33, 95% CI 0.48 to 3.70 **Additional uterotonics:** 10/100 (10%) with misoprostol *v* 7/100 (7%) with methylergometrine, RR 1.43, 95% CI 0.57 to 3.60 **Manual placenta removal and third stage greater than 30 minutes:** no events in either group	**Nausea:** 20/100 (20%) with misoprostol *v* 30/100 (30%) with methylergometrine, RR 0.67, 95% CI 0.41 to 1.09 **Vomiting**: 19/100 (19%) with misoprostol *v* 30/100 (30%) with methylergometrine, RR 0.63, 95% CI 0.38 to 1.05 **Diarrhoea**: 3/100 (3%) with misoprostol *v* 3/100 (3%) with methylergometrine, RR 1.00, 95% CI 0.21 to 4.84 **Shivering:** 31/100 (31%) with misoprostol *v* 10/100 (10%) with methylergometrine, RR 3.10, 95% CI 1.61 to 5.98 **Fever (at least 38 °C):** 29/100 (29%) with misoprostol *v* 7/100 (7%) with methylergometrine, RR 4.14, 95% CI 1.90 to 9.01
[16] 1 RCT	2023 women in India: oral misoprostol (400 micrograms) versus oxytocin IM (10 IU) versus ergometrine IV (0.2 mg).	**Severe postpartum haemorrhage at least 1000 mL):** 1/730 (1%) with misoprostol *v* 12/1293 (0.8%) with ergometrine, RR 0.18, 95% CI 0.02 to 1.38 **Postpartum haemorrhage (at least 500 mL):** 19/730 (3%) with misoprostol *v* 13/617 (2%) with ergometrine, RR 1.24, 95% CI 0.62 to 2.48 **Blood loss:** mean: 192.5 mLwith misoprostol *v* 183 mL with ergometrine, WMD 9.50, 95% CI –4.48 to +23.48 **Additional uterotonics:** 63/730 (9%) with misoprostol *v* 38/617 (6%) with ergometrine, RR 1.40, 95% CI 0.95 to 2.07 **Blood transfusion:** 1/730 (0.1%) with misoprostol *v* 2/617 (0.3%) with ergometrine, RR 0.42, 95% CI 0.04 to 4.65 **Duration of third stage; mean minutes:** 4.87 with misoprostol *v* 4.37 with ergometrine, WMD 0.50, 95% CI –0.03 to +1.03	**Nausea:** 5/730 (1%) with misoprostol *v* 11/617 (2%) with ergometrine RR 0.38, 95% CI 0.13 to 1.10 **Vomiting:** 6/730 (0.8%) with misoprostol *v* 2/617 (0.3%) with ergometrine, RR 2.54, 95% CI 0.51 to 12.52 **Diarrhoea:** 1/730 (0.1%) with misoprostol *v* 0/617 (0%) with ergometrine, RR 2.54, 95% CI 0.10 to 62.15 **Severe shivering:** 2/730 (0.3%) with misoprostol *v* 0/617 (0%) with ergometrine, RR 4.23, 95% CI 0.20 to 87.88 **Shivering**: 68/730 (9%) with misoprostol *v* 14/617 (2%) with ergometrine, RR 4.11, 95% CI 2.33 to 7.22

TABLE 4 **Oral misoprostol versus oxytocin**

RCT	Population/ Intervention	Results	Adverse effects
[16] Australia 1999	930 women with vaginal delivery: oral misoprostol (400 micrograms) *v* oxytocin (10 IU im)	**Severe postpartum haemorrhage (at least 1000 mL):** 13/424 (3%) with misoprostol *v* 7/439 (2%) with oxytocin; RR 1.92, 95% CI 0.77 to 4.77 **Postpartum haemorrhage (at least 500 mL):** 63/424 (15%) with misoprostol *v* 24/439 (6%) with oxytocin; RR 2.72, 95% CI 1.73 to 4.27 **Additional uterotonics:** 95/424 (22%) with misoprostol *v* 34/439 (8%) with oxytocin, RR 2.89, 95% CI 2.00 to 4.18 **Blood transfusion:** 5/424 (1%) with misoprostol *v* 5/439 with oxytocin (1%), RR 1.04, 95% CI 0.30 to 3.55 **Manual removal of placenta:** 0 events in each group	**Vomiting**: 8/424 (2%) with misoprostol *v* 15/439 (4%) with oxytocin; RR 0.55, 95% CI 0.24 to 1.29 **Diarrhoea**: 1/424 (0.2%) with misoprostol *v* 0/439 (0%) with oxytocin; RR 3.11, 95% CI 0.13 to 76.03 **Shivering:**79/424 (169%) with misoprostol *v* 31/439 (7%) with oxytocin; RR 2.64, 95% CI 1.78 to 3.91
[16] Canada 2005	622 women with vaginal delivery: oral misoprostol (400 micrograms) *v* oxytocin (5 IU im)	**Maternal death**: 0 events in each group **Severe postpartum haemorrhage (at least 1000 mL):** 14/311 (5%) with misoprostol *v* 7/311 (2%) with oxytocin; RR 2.00, 95% CI 0.82 to 4.89 **Additional uterotonics**: 159/311 (51%) with misoprostol *v* 126/311 (40%) with oxytocin; RR 1.26, 95% CI 1.06 to 1.50 **Blood transfusions:** 0 events in either group **Manual removal of the placenta:** 25/311 (8%) with misoprostol *v* 25/311 (8%) with oxytocin; RR 1.00, 95% CI 0.59 to 1.70	**Shivering:** 21/311 (7%) with misoprostol *v* 0/311 (0%) with oxytocin; RR 43.0, 95% CI 2.62 to 706.74 **Fever (at least 38 °C):** 39/311 (13%) with misoprostol *v* 0/311 (0%) with oxytocin; RR 4.88 to 1279.63
[16] France 2001	602 women with vaginal delivery: oral misoprostol (600 micrograms) *v* oxytocin (2.5 IU iv)	**Severe postpartum haemorrhage (at least 1000 mL):** 16/186 (9%) with misoprostol *v* 12/189 (6%) with oxytocin, RR 1.41, 95% CI 0.68 to 2.89 **Postpartum haemorrhage (at least 500 mL):** 52/186 (30%) with misoprostol *v* 29/196 (15%) with oxytocin, RR 1.89, 95% CI 1.26 to 2.84	**Vomiting**: 7/186 (4%) with misoprostol *v* 1/196 (0.3%) with oxytocin, RR 7.38, 95% CI 0.92 to 59.38 **Shivering**: 66/86 (77%) with misoprostol *v* 38/94 (40%), RR 11.59, 95% CI 0.65 to 208.12 **Fever (at least 38 °C):** 6/186 (3%) with misoprostol *v* 0/196 (0%) with oxytocin, RR 13.70, 95% CI 0.78 to 241.41
[16] Ghana 2001	401 women with vaginal delivery: oral misoprostol (400 micrograms) *v* oxytocin (10 IU iv)	**Severe postpartum haemorrhage (at least 1000 mL):** 0 events in each group **Postpartum haemorrhage (at least 500 mL):** 0/202 (0%) with misoprostol *v* 2/196 (1%); RR 0.19, 95% CI 0.01 to 4.02 **Additional uterotonics**: 6/168 (4%) with misoprostol *v* 8/172 (5%) with oxytocin, RR 0.77, 95% CI 0.27 to 2.17 **Blood transfusion**: 0/136 (0%) with misoprostol *v* 1/138 (0.7%), RR 0.34, 95% CI 0.01 to 8.23 **Manual removal of placenta**: 1/182 (0.5%) with misoprostol *v* 1/187 (0.5%), RR 1.03, 95% CI 0.06 to 16.30	**Nausea:** 5/152 (3%) with misoprostol *v* 6/159 (4%) with oxytocin RR 0.87, 95% CI 0.27 to 2.80 **Vomiting**: 5/164 (3%) with misoprostol *v* 4/177 (2%) with oxytocin, RR 1.35, 95% 0.37 to 4.94 **Diarrhoea**: 2/146 (1%) with misoprostol *v* 5/156 (3%) with oxytocin, RR 0.43, 95% 0.08 to 2.17 **Shivering**: 39/176 (22%) with misoprostol *v* 10/176 (6%), RR 3.90, 95% 2.01 to 7.57
[16] Ghana 2006	450 women with vaginal delivery: oral misoprostol (800 micrograms) *v* oxytocin (10 IU im)	**Maternal death**: 0 events in each group **Severe postpartum haemorrhage (at least 1000 mL):** 0/2255 with misoprostol *v* 0/225 with oxytocin **Postpartum haemorrhage (at least 500 mL)** 0/225 (0%) with misoprostol *v* 5/225 (2%) with oxytocin **Additional uterotonics:** 16/225 (7%) with misoprostol *v* 21/225 (9%) with oxytocin, RR 0.76, 95% CI 0.41 to 1.42 **Blood transfusion:** 1/222 (0.5%) with misoprostol *v* 2/221 (0.9%) with oxytocin, RR 0.580, 95% CI 0.05 to 5.45 **Manual removal of placenta**: 0 events in each group	**Nausea:** 2/223 (1%) with misoprostol *v* 4/222 (2%) with oxytocin, RR 0.50, 95% CI 0.09 to 2.69 **Vomiting**: 1/221 (0.5%) with misoprostol *v* 4/224 (2%) with oxytocin, RR 0.25, 95% CI 0.03 to 2.25 **Diarrhoea:** 5/221 (2%) with misoprostol *v* 0/218 (0%) RR 10.85, 95% CI 0.60 to 195.06 **Shivering:** 180/223 (80%) with misoprostol *v* 8/223 (4%) with oxytocin, RR 22.50, 95% CI 11.36 to 44.56

RCT	Population/ Intervention	Results	Adverse effects
[16] India 2006	2023 women with vaginal delivery: oral misoprostol (400 micrograms) *v* oxytocin (10 IU iv)	**Severe postpartum haemorrhage (at least 1000mL):** 1/730 (0.1%) with misoprostol *v* 10/1293 (8%), RR 0.18, 95% CI 0.02 to 1.38 **Postpartum haemorrhage (at least 500 mL):** 19/170 (3%) with misoprostol *v* 13/617 (2%) with oxytocin, RR 1.24, 95% CI 0.62 to 2.48 **Additional uterotonics:** 63/730 (9%) with misoprostol *v* 38/617 (6%) with oxytocin, RR 1.40, 95% 0.95 to 2.07 **Blood transfusion:** 1/730 (0.1%) with misoprostol *v* 2/617 (0.3%) with oxytocin, RR 0.42, 95% CI 0.04 to 4.65	**Nausea:** 5/730 (1%) with misoprostol *v* 11/617 (2%) , RR 0.38, 95% CI 0.13 to 1.10 **Vomiting:** 6/730 (0.8%) with misoprostol *v* 2/617 (0.3%) with oxytocin, RR 2.54, 95% CI 0.51 to 12.52 **Diarrhoea**: 1/730 (0.1%) with misoprostol *v* 0/617 (0%) with oxytocin, RR 1.24, 95% CI 0.10 to 62.15 **Shivering:** 68/730 (9%) with misoprostol *v* 14/617 (2%) with oxytocin, RR 4.11, 95% CI 2.33 to 7.22 **Severe Shivering:** 2/730 (0.3%) with misoprostol *v* 0/617 (0%) with oxytocin, RR 4.23, 95% CI 0.20 to 87.88
[16] Nigeria 2003	496 women with vaginal delivery: oral misoprostol (600 micrograms) *v* oxytocin (10 IU im)	**Severe postpartum haemorrhage (at least 1000 mL):** 0 events in each group **Postpartum haemorrhage (at least 500 mL):** 8/100 (8%) with misoprostol *v* 6/100 (6%) with oxytocin; RR 1.33, 95% CI 0.48 to 3.70 **Additional uterotonics:** 31/247 (13%) with misoprostol *v* 27/249 (6%) with oxytocin, RR 1.16, 95% CI 0.71 to 1.88 **Blood transfusion:** 0 events in each group **Manual removal of the placenta:** 4/247 (2%) with misoprostol *v* 2/249 (1%), RR 2.02, 95% CI 0.37 to 10.91	**Nausea:** 8/247 (3%) with misoprostol *v* 10/249 (4%) with oxytocin, RR 0.81, 95% CI 0.32 to 2.01 **Vomiting:** 12/247 (5%) with misoprostol *v* 9/249 (4%) RR 1.34, 95% CI 0.58 to 3.13 **Diarrhoea:** 7/247 (3%) with misoprostol *v* 2/249 (1%) with oxytocin, RR 3.53, 95% CI 0.74 to 16.82 **Shivering:** 141/247 (57%) with misoprostol *v* 35/249 (14%) with oxytocin, RR 4.06, 95% CI 2.93 to 5.62 **Severe Shivering:** 3/247 (1%) with misoprostol *v* 1/249 (0.4%) with oxytocin, RR 3.02, 95% CI 0.32 to 28.88
[16] Turkey 2003	1800 women with vaginal delivery: oral misoprostol (400 micrograms) *v* oxytocin (10 IU iv)	**Severe postpartum haemorrhage (at least 1000 mL):** 14/388 (4%) with misoprostol *v* 15/384 (4%) with oxytocin, RR 0.92, 95% CI 0.45 to 1.89 **Postpartum haemorrhage (at least 500 mL):** 35/388 (9%) with misoprostol *v* 28/384 (7%) with oxytocin, RR 1.24, 95% CI 0.77 to 1.99 **Blood transfusion:** 14/388 (4%) with misoprostol *v* 13/384 (3%) with oxytocin, RR 1.07, 95% CI 0.51 to 2.24	**Vomiting**: 4/388 (1%) with misoprostol *v* 3/384 (0.7%) with oxytocin, RR 1.32, 95% CI 0.30 to 5.86 **Diarrhoea:** 15/388 (4%) with misoprostol *v* 12/384 (3%) with oxytocin, RR 1.24, 95% 0.59 to 2.61 **Shivering:** 44/388 (11%) with misoprostol *v* 19/384 (5%) with oxytocin, RR 1.36 to 3.85 **Fever (at least 38 °C):** 17/388 (4%) with misoprostol *v* 5/384 (1%) with oxytocin, RR 3.36, 95% CI 2.55 to 140.96

RCT	Population/ Intervention	Results	Adverse effects
[16] WHO 1999	597 women with vaginal delivery: oral misoprostol 400 or (600 micrograms *v* oxytocin (10 IU iv)	**Oral misoprostol (400 micrograms)** **Maternal death:** 0 events in each group **Severe postpartum haemorrhage (at least 1000 mL):** 14/198 (7%) with misoprostol *v* 13/200 (7%) with oxytocin, RR 1.09, 95% CI 0.52 to 2.25 **Postpartum haemorrhage (at least 500 mL):** 51/198 (26%) with misoprostol *v* 52/200 (26%) with oxytocin, RR 0.99, 95% CI 0.71 to 1.38 **Additional uterotonics**: 23/198 (12%) with misoprostol *v* 28/200 (14%) with oxytocin, RR 0.83, 95% CI 0.50 to 1.39 **Blood transfusion:** 0 events in each group **Manual removal of placenta:** 4/198 (2%) with misoprostol *v* 8/200 (4%) with oxytocin, RR 0.51, 95% CI 0.15 to 1.65 **Oral misoprostol (600 micrograms)** **Maternal death:** 0 events in each group **Severe postpartum haemorrhage (at least 1000 mL):** 8/199 (4%) with misoprostol *v* 13/200 (7%) with oxytocin, RR 0.62, 95% CI 0.26 to 1.46 **Postpartum haemorrhage (at least 500 mL):** 45/199 (23%) with misoprostol *v* 52/200 (26%), RR 0.87, 95% CI 0.61 to 1.23 **Additional uterotonics:** 18/199 (9%) with misoprostol *v* 28/200 (14%) with oxytocin, RR 0.45, 95% CI 0.37 to 1.13 **Blood transfusion:** 0 events in each group **Manual removal placenta:** 3/199 (2%) *v* 8/200 (4%), RR 0.38, 95% CI 0.10 to 1.40	**Oral misoprostol (400 micrograms)** **Nausea:** 0/198 (0%) with misoprostol v 1/200 (0.5%) with oxytocin, RR 0.34, 95% CI 0.01 to 8.22 **Vomiting:** 0/198 (0%) with misoprostol *v* 1/200 (0.5%) with oxytocin, RR 0.34, 95% CI 0.01 to 8.22 **Diarrhoea**: 0 events in each group **Shivering:** 38/198 (19%) with misoprostol *v* 25/200 (13%) with oxytocin, RR 1.54, 95% CI 0.96 to 2.44 **Severe shivering:** 0 events in each group **Fever (at least 38 °C):** 4/195 (2%) with misoprostol *v* 6/199 (3%) with oxytocin, RR 0.68, 95% CI 0.19 to 2.37 **Oral misoprostol (600 micrograms)** **Nausea:** 1/199 (0.5%) with misoprostol *v* 1/200 (0.5%) with oxytocin, RR 1.01, 95% CI 0.06 to 15.96 **Vomiting:** 0/199 (0%) with misoprostol v 1/200 (0.5%) with oxytocin, RR 0.34, 95% CI 0.01 to 8.17 **Diarrhoea:** 4/199 (2%) with misoprostol *v* 0/200 (0%) with oxytocin, RR 0.49 to 166.9 **Shivering:** 56/199 (28%) with misoprostol *v* 25/200 (13%) with oxytocin, RR 2.25, 95% CI 1.47 to 3.46 **Severe shivering:** 3/199 (2%) with misoprostol *v* 0/200 (0%), RR 7.04, 95% CI 0.37 to 135.32 **Fever (at least 38 °C):** 15/199 (8%) with misoprostol *v* 6/199 (3%) with oxytocin, RR 2.5, 95% CI 0.99 to 6.31
[16] WHO 2001	18530 women with vaginal delivery: oral misoprostol (600 micrograms) *v* oxytocin (10 IU iv/im)	**Maternal death:** 2/9264 (0.01%) with misoprostol *v* 2/9266 (0.02%) with oxytocin, RR 1, 95% CI 0.14 to 7.10 **Severe postpartum haemorrhage (at least 1000 mL):** 366/9214 (4%) with misoprostol *v* 263/9228 (3%) with oxytocin, RR 1.19, 95% CI 1.19 to 1.63 **Postpartum haemorrhage (at least 500 mL):** 1793/9213 (20%) with misoprostol *v* 1248/9227 (14%) with oxytocin, RR 1.44, 95% CI 1.35 to 1.54 **Additional uterotonics:** 1398/9225 (15%) with misoprostol *v* 1002/9228 (11%) with oxytocin, RR 1.40, 95% CI 1.29 to 1.51 **Blood transfusion:** 72/9221 (0.8%) with misoprostol *v* 97/9226 (1%) with oxytocin, RR 0.74, 95% CI 0.55 to 1.02 **Manual removal of placenta:** 219/9225 (2%) with misoprostol *v* 215/9232 (2%) with oxytocin, RR 1.02, 95% CI, 0.85 to 1.23	**Nausea:** 77/9227 (0.8%) with misoprostol *v* 34/9228 (0.4%) with oxytocin, RR 2.27, 95% CI 1.52 to 3.39 **Vomiting**: 66/9227 (0.7%) with misoprostol *v* 25/9232 (0.3%) with oxytocin, RR 2.64, 95% CI 1.67 to 4.18 **Diarrhoea:** 35/9227 (0.4%) with misoprostol *v* 8/9232 (0.1%) with oxytocin, RR 4.38, 95% CI 2.03 to 9.43 **Shivering:** 1620/9227 (18%) with misoprostol *v* 466/9232 (5%) with oxytocin, RR 3.48, 95% CI 3.15 to 3.84 **Severe Shivering:** 120/9227 (1%) with misoprostol *v* 14/9232 (0.2%) with oxytocin , RR 8.58, 95% CI 4.93 to 14.91 **Fever (at least 38 °C):** 559/9198 (6%) with misoprostol *v* 78/9205 (1%) with oxytocin RR 7.17, 95% CI 5.67 to 9.07
[16] Zimbabwe 2001	500 women with vaginal delivery: oral misoprostol (400 micrograms) *v* oxytocin (10 IU im)	**Severe postpartum haemorrhage (at least 1000mL):** 9/243 (4%) with misoprostol *v* 5/256 (2%) with oxytocin **Postpartum haemorrhage (at least 500 mL):** 36/243 (15%) with misoprostol *v* 34/256 (13%) with oxytocin, RR 1.15, 95% CI 0.74 to 1.76 **Additional uterotonics:** 13/243 (5%) with misoprostol *v* 7/256 (3%) with oxytocin, RR 1.96, 95% CI 0.79 to 4.82 **Blood transfusion:** 2/243 (0.8%) with misoprostol *v* 1/256 (0.4%) with oxytocin, RR 2.11, 95% CI 0.19 to 23.09 **Manual removal of placenta:** 3/243 (1.2%) with misoprostol *v* 2/256 (0.8%) with oxytocin, RR 1.58, 95% CI 0.27 to 9.38	**Nausea:** 7/243 (3%) with misoprostol *v* 5/256 (2%) with oxytocin, RR 1.47, 95% CI 0.47 to 4.58 **Vomiting:** 2/243 (1%) with misoprostol *v* 1/256 (0.4%) with oxytocin, RR 3.16, 95% CI 0.33 to 30.18 **Shivering:** 106/243 (44%) with misoprostol *v* 78/256 (22%) with oxytocin, RR 1.43, 95% CI 1.13 to 1.81 **Fever (at least 38 °C):** 18/243 (7%) with misoprostol *v* 1/256 (0.4%) with oxytocin, RR 18.96, 95% CI 2.55 to 140.96

RCT	Population/ Intervention	Results	Adverse effects
[16] London	40 women with elective or emergency caesarean: oral misoprostol (500 micrograms) *v* oxytocin (10 IU iv)	**Severe postpartum haemorrhage (at least 1000 mL):** 3/20 (15%) with misoprostol *v* 3/20 (15%) with oxytocin, RR 1.00, 95% CI 0.23 to 4.37 **Postpartum haemorrhage (at least 500 mL):** 17/20 (85%) with misoprostol *v* 17/20 (85%) with oxytocin, RR 1.00, 95% CI 0.77 to 1.30 **Additional uterotonics:** 6/20 (30%) with misoprostol *v* 1/20 (5%) with oxytocin, RR 6.00, 95% CI 0.79 to 45.42	**Shivering:** 13/20 (65%) with misoprostol *v* 8/20 (40%) with oxytocin, RR 1.63, 95% CI 0.87 to 3.04 **Severe Shivering:** 4/20 (20%) with misoprostol *v* 0/20 (0%) with oxytocin, RR 9.00, 95% CI 0.52 to 156.91
[31]	56 women with caesarean section in Switzerland: oral misoprostol (800 micrograms) *v* oxytocin (20 IU)	**Calculated blood loss:** 1083 mL with misoprostol *v* 970 mL with oxytocin	**Shivering:** 10/28 (36%) with misoprostol *v* 2/25 (8%) with oxytocin, RR 4.46, 95 CI 1.08 to 18.45

TABLE 5 **Oral misoprostol *v* oxytocin/ergometrine combinations**

RCT	Population/ Intervention	Results	Adverse Effects
[16] Australia 1999	930 women with vaginal delivery: oral misoprostol (400 micrograms) *v* oxytocin (5 IU iv) plus ergometrine (0.5 mg)	**Severe postpartum haemorrhage (at least 1000 mL):** 12/296 (4%) with misoprostol *v* 7/310 (2%) with combination therapy, RR 1.80, 95% CI 0.72 to 4.50 **Postpartum haemorrhage (at least 500 mL):** 61/296 (21%) with misoprostol *v* 23/310 (7%) with combination therapy, RR 2.78, 95% CI 1.77 to 4.37 **Additional uterotonics:** 59/296 (20%) with misoprostol *v* 23/310 (9%) with combination therapy, RR 2.21, 95% CI 1.45 to 3.36 **Blood transfusion:** 4/296 (1%) with misoprostol *v* 3/310 (1%) with combination therapy, RR 1.40, 95% CI 0.23 to 6.19	None reported
[16] Hong Kong 2001	2058 women with vaginal delivery: oral misoprostol (600 micrograms) *v* oxytocin (5 IU im) plus ergometrine (0.5 mg)	**Severe postpartum haemorrhage (at least 1000 mL):** 5/1026 (0.5%) with misoprostol *v* 4/1032 (0.4%) with combination therapy, RR 1.26, 95% CI 0.34 to 4.67 **Postpartum haemorrhage (at least 500 mL):** 60/1026 (6%) with misoprostol *v* 44/1032 (4%) with combination therapy, RR 1.37, 95% CI 0.94 to 2.00 **Additional uterotonics:** 232/1026 (23%) with misoprostol *v* 144/1032 (14%) with combination therapy, RR 1.62, 95% CI 1.34 to 1.96 **Blood transfusion:** 15/1026 (2%) with misoprostol *v* 16/1032 (2%) with combination therapy, RR 0.94, 95% CI 0.47 to 1.90 **Manual removal of placenta:** 4/1026 (0.4%) with misoprostol v 14/1032 (1.4%), RR 0.29, 95% CI 0.09 to 0.87	**Nausea:** 20/1026 (2%) with misoprostol *v* 27/1032 (3%) with combination therapy, RR 0.81, 95 % CI 0.40 to 1.63 **Vomiting:** 14/1026 (1%) with misoprostol *v* 23/1032 (2%) with combination therapy, RR 0.61, 95% CI 0.32 to 1.18 **Headache:** 81/1026 (8%) with misoprostol *v* 83/1032 (8%) with combination therapy, RR 0.98, 95% CI 0.71 to 1.35 **Shivering:** 310/1026 (30%) with misoprostol *v* 102/1032 (10%) with combination therapy, RR 3.06, 95% CI 2.49 to 3.76 **Fever (at least 38 °C)**: 87/1026 (9%) with misoprostol *v* 13/1032 (1%) with combination therapy, RR 6.73, 95% CI 3.78 to 11.98
[16] Turkey 2003	1800 women with vaginal delivery: oral misoprostol (400 micrograms) *v* oxytocin (10 IU iv) plus methylergometrine (1 mL im)	**Severe postpartum haemorrhage (at least 1000 mL):** 14/388 (4%) with misoprostol *v* 5/398 (1%) with combination therapy, RR 2.87, 95% CI 1.04 to 7.90 **Postpartum haemorrhage (at least 500 mL):** 35/388 (9%) with misoprostol *v* 14/398 (4%) with combination therapy, RR 2.56, 95% CI 1.40 to 4.69 **Additional uterotonics:** 42/388 (10%) with misoprostol *v* 13/398 (3%) with combination therapy, RR 3.31, 95% CI 1.81 to 6.08 **Blood Transfusion:** 14/388 (4%) with misoprostol *v* 6/398 (2%) with combination therapy, RR 2.39, 95% CI 0.93 to 6.16	**Vomiting**: 4/388 (1%) with misoprostol *v* 5/398 (1%) with combination therapy, RR 0.82, 95% CI 0.22 to 3.03 **Diarrhoea:** 15/388 (4%) with misoprostol *v* 17/398 (4%) with combination therapy, RR 0.91, 95% CI 0.46 to 1.79 **Shivering**: 44/388 (11%) with misoprostol *v* 15/398 (4%) with combination therapy, RR 3.01, 95% CI 1.70 to 5.32 **Fever (at least 38 °C):** 17/388 (4%) with misoprostol *v* 6/398 (2%) with combination therapy, RR 2.91, 95% CI 1.16 to 7.29
[16] Hong Kong 2006	355 women: oral misoprostol (400 micrograms) *v* syntomertine (1 mL: oxytocin [5 IU] plus ergometrine [0.5 mg])	**Severe postpartum haemorrhage (at least 1000 mL):** 2/178 (1%) with misoprostol *v* 1/177 (0.6%) with combination therapy, RR 1.99, 95 % CI 0.18 to 21.74 **Postpartum haemorrhage (at least 500 mL):** 18/178 (10%) with misoprostol *v* 9/177 (5%) with combination therapy, RR 1.99, 95% CI 092 to 4.31 **Additional uterotonics:** 41/178 (23%) with misoprostol *v* 24/177 (13%) with combination therapy, RR 1.70, 95% CI 1.07 to 2.69 **Blood transfusion:** 8/178 (5%) with misoprostol *v* 4/177 (2%) with combination therapy, RR 1.99, 95% CI 0.61 to 6.49 **Manual placenta removal:** 3/178 (2%) with misoprostol *v* 7/177 (4%) with combination therapy, RR 0.43, 95% CI 0.11 to 1.62	**Nausea:** 13/178 (7%) with misoprostol *v* 16/177 (9%) with combination therapy, RR 0.81, 95% CI 0.40 to 1.63 **Vomiting:** 7/178 (4%) with misoprostol *v* 20/177 (11%) with combination therapy, RR 0.35, 95% CI 0.15 to 0.80 **Diarrhoea**: 0 events in each group Headache: 8/178 (5%) with misoprostol *v* 2/177 (1%) with combination therapy, RR 4.12, 95% CI 0.86 to 19.67 **Shivering:** 35/178 (20%) with misoprostol *v* 2/177 (1%) with combination therapy, RR 17.4, 95% CI 4.25 to 71.25 **Fever (at least 38 °C)**: 7/178 (4%) with misoprostol *v* 0/177 (0%) with combination therapy, RR 14.92, 95% 0.86 to 259.21

TABLE 6 **Rectal misoprostol *v* placebo/no intervention/oxytocin comparisons/oxytocin plus ergometrine/carboprost injections**

RCT	Population/ Intervention	Results	Adverse effects
[16] South Africa 1998	550 low-risk women in South Africa: rectal misoprostol (400 micrograms) *v* placebo	**Severe postpartum haemorrhage (at least 1000 mL):** 13/270 (5%) with misoprostol *v* 19/272 (7%) with placebo; RR 0.69, 95% CI 0.35 to 1.37 **Additional medical treatment:** 9/271 (3%) with misoprostol *v* 13/275 (5%) with placebo; RR 0.70, 95% CI 0.31 to 1.62 **Manual removal of placenta:** one woman in the rectal misoprostol group	**Vomiting:** 1/271 (0.4%) with misoprostol *v* 1/275 (0.4%) with placebo; RR 1.01, 95% CI 0.06 to 16.14 **Shivering:** 1/34 (3%) with misoprostol *v* 4/36 (11%) with placebo; RR 0.26, 95% CI 0.03 to 2.25 **Abdominal pain:** 1/271 (0.4%) with misoprostol *v* 0/275 (0%) with placebo; RR 3.04, 95% CI 0.12 to 74.40
[16] Canada 2002	223 women with vaginal delivery: rectal misoprostol (400 micrograms) *v* oxytocin (10 IU iv or im)	**Additional uterotonics:** 28/110 (25%) with misoprostol *v* 20/113 (18%) with oxytocin, RR 1.44, 95% CI 0.86 to 2.40 **Blood transfusion:** 0 events in each group **Manual removal of placenta:** 1/110 (0.9%) with misoprostol *v* 6/113 (5%) with oxytocin, RR 0.17, 95% CI 0.02 to 1.40	**Vomiting:** 6/105 (6%) with misoprostol *v* 4/110 (4%) with oxytocin, RR 1.57, 95% CI 0.46 to 5.41 **Shivering:** 26/105 (25%) with misoprostol *v* 15/110 (14%) with oxytocin, RR 1.82, 95% CI, 1.02 to 3.23 **Fever (at least 38 °C):** 20/107 (19%) with misoprostol *v* 12/112 (11%) with oxytocin, RR 1.74, 95% CI 0.90 to 3.39 **Nausea:** 8/105 (8%) with misoprostol *v* 5/110 (5%) with oxytocin, RR 1.68, 95% CI 0.57 to 4.96 **Abdominal pain:** 12/105 (11%) with misoprostol *v* 13/110 (12%) with oxytocin, RR 0.97, 95% CI 0.46 to 2.02 **Headache:** 9/105 (9%) with misoprostol v 4/100 (4%) with oxytocin, RR 2.36, 95% CI 0.75 to 7.42
[16] Turkey 2002	1663 women with vaginal delivery: rectal misoprostol (400 micrograms) *v* oxytocin (10 IU iv)	**Severe postpartum haemorrhage (at least 1000 mL):** 17/396 (4%) with misoprostol *v* 14/407 (3%) with oxytocin, RR 1.25, 95% CI 0.62 to 2.50 **Postpartum haemorrhage (at least 500 mL):** 33/396 (8%) with misoprostol *v* 33/407 (8%) with oxytocin, RR 1.03, 95% CI 0.65 to 1.63 **Blood transfusion:** 12/396 (3%) with misoprostol *v* 13/407 (3%) with oxytocin, RR 0.95, 95% CI 0.44 to 2.05	**Vomiting:** 2/396 (0.5%) with misoprostol *v* 2/407 (0.5%) with oxytocin, RR 1.03, 95% CI 0.15 to 7.26 **Diarrhoea:** 11/396 (3%) with misoprostol *v* 9/407 (2%) with oxytocin, RR 1.26, 95% CI 0.53 to 3.00 **Shivering:** 47/396 (12%) with misoprostol *v* 16/407 (4%) with oxytocin, RR 3.02, 95% CI 3.02, 95% CI 1.74 to 5.23 **Fever (at least 38 °C):** 16/396 (4%) with misoprostol *v* 6/407 (2%) with oxytocin, RR 2.47, 95% CI 1.08 to 6.93
[16] Mozam-bique 2001	633 women with vaginal delivery: rectal misoprostol (400 micrograms) *v* oxytocin (10 IU im)	**Severe postpartum haemorrhage (at least 1000 mL):** 0/323 (0%) with misoprostol *v* 1/339 (0.3%) with oxytocin, RR 0.35, 95% CI 0.01 to 8.56 **Postpartum haemorrhage (at least 500 mL):** 10/323 (3%) with misoprostol *v* 15/339 (4%) with oxytocin, RR 0.70, 95% CI 0.32 to 1.53 **Additional uterotonics:** 7/323 (2%) with misoprostol *v* 7/339 (2%) with oxytocin, RR 1.05, 95% CI 0.37 to 2.96 **Blood transfusion:** 2/323 (0.6%) with misoprostol *v* 1/339 (0.3%) with oxytocin, RR 2.10, 95% CI 0.19 to 23.04	**Vomiting:** 2/323 (0.6%) with misoprostol *v* 1/337 (0.3%) with oxytocin, RR 2.09, 95% CI 0.19 to 22.90 **Diarrhoea:** 0/323 (0%) with misoprostol *v* 2/338 (0.6%) with oxytocin, RR 0.21, 95% CI 0.01 to 4.34 **Shivering:** 113/323 (38%) with misoprostol *v* 51/337 (15%) with oxytocin, RR 2.52, 95% CI 1.89 to 3.36
[16] USA 2001	400 women with vaginal delivery: rectal misoprostol (400 micrograms) *v* oxytocin (20 IU)	**Severe postpartum haemorrhage (at least 1000 mL):** 15/154 (10%) with misoprostol *v* 14/161 (9%) with oxytocin, RR 1.12, 95% CI 0.56 to 2.24 **Postpartum haemorrhage (at least 500 mL):** 70/154 (45%) with misoprostol *v* 61/161 (38%) with oxytocin, RR 1.20, 95% CI 0.92 to 1.56 **Additional uterotonics:** 36/159 (23%) with misoprostol *v* 18/166 (11%) with oxytocin, RR 2.09, 95% CI 1.24 to 3.52 **Blood transfusion:** 2/159 (1%) with misoprostol *v* 2/166 (1%) with oxytocin, RR 1.04, 95% CI 0.15 to 7.32	**Shivering**: 7/159 (4%) with misoprostol *v* 7/166 (4%) with oxytocin, RR 1.04, 95 CI 0.37 to 2.91

RCT	Population/ Intervention	Results	Adverse effects
[16] South Africa 1998	491 women at low risk of postpartum haemorrhage in South Africa: rectal misoprostol (400 micrograms) *v* ergometrine plus oxytocin (1 ampoule syntometrine im).	**Postpartum haemorrhage (at least 500 mL):** 2/231 (0.9%) with misoprostol *v* 1/233 (0.4%) with syntometrine, RR 2.02, 95% CI 0.18 to 22.09	None reported
[16] Turkey	793 women with vaginal delivery in Turkey: rectal misoprostol (400 micrograms) versus oxytocin IV (10 IU) plus methylergometrine IM (1mL).	**Severe postpartum haemorrhage (at least 1000 mL):** 17/396 (4%) with misoprostol *v* 7/402 (2%) with syntometrine, RR 2.47, 95% CI 1.03 to 5.88) **Postpartum haemorrhage (at least 500 mL):** 39/396 (10%) with misoprostol *v* 14/402 (4%) syntometrine, RR 2.83, 95% CI 1.56 to 5.13 **Additional uterotonic:** 51/396 (12%) with misoprostol *v* 15/402 (4%) with syntometrine, RR 3.45, 95% CI 1.97 to 6.03 **Blood transfusion:** 12/396 (3%) with misoprostol *v* 4/402 (1%) with syntometrine, RR 3.11, 95% CI 0.99 to 9.72	**Shivering**: 47/396 (12%) with misoprostol *v* 19/402 (5%) with syntometrine, RR 2.51, 95% CI 1.50 to 4.20 **Fever (at least 38 °C):** 16/396 (4%) with misoprostol *v.* 6/402 (2%) with syntometrine, RR 2.71, 95% CI 1.04 to 6.85 **Vomiting**: 2/396 (0.5%) with misoprostol *v* 1/402 (0.2%) with syntometrine, RR 2.03, 95% CI 0.18 to 22.30 **Diarrhoea**: 11/396 (3%) with misoprostol *v* 10/402 (3%) with syntometrine, RR 1.12, 95% CI 0.48 to 2.60
[16] India	120 full-term, low-risk women in rural India: rectal misoprostol (400 micrograms) versus 15-methyl prostaglandin F2-alpha (125 micrograms)	**Postpartum haemorrhage (at least 500 mL):** 4/60 (0.6%) with misoprostol *v* 3/60 (0.6%) with prostaglandin F2-alpha, RR 1.33, 95% CI 0.31 to 5.70 **Additional oxytocics**: 10/60 (17%) misoprostol *v* 2/60 (3%) prostaglandin F2-alpha, RR 5.0, 95% CI 1.14 to 21.86 **Blood transfusion:** One woman in the misoprostol group	**Gastrointestinal adverse effects (nausea, vomiting, and diarrhoea):** 3/60 (5%) with misoprostol *v* 11/60 (18%) with 15-methyl prostaglandin F2-alpha, RR 0.27, 95% CI 0.08 to 0.93 **Shivering:** Five women in the misoprostol group and none in the injected prostaglandin group (P = 0.06)

TABLE **GRADE evaluation of interventions for postpartum haemorrhage: prevention**

Important outcomes			Morbidity, need for further interventions, mortality, adverse effects						
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of non-drug interventions to prevent primary postpartum haemorrhage?									
At least 5 RCTs (at least 6477 women) [4]	Morbidity	Active management *v* expectant management alone or combined with oxytocin	4	0	0	0	0	High	Effect-size point added for RR less than 0.5
At least 5 RCTs (at least 6477 women) [4]	Need for further interventions	Active management *v* expectant management alone or combined with oxytocin	4	0	0	0	0	High	
At least 5 RCTs (at least 6477 women) [4]	Adverse effects	Active management *v* expectant management alone or combined with oxytocin	4	0	0	0	0	High	
2 (1948) [6] [7]	Morbidity	Controlled cord traction *v* minimal intervention	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for differences in timing and mode of oxytocin administration
1 (477) [8]	Morbidity	Controlled cord traction plus immediate cord drainage *v* expectant management	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting. Consistency point deducted for lack of consistent benefit
1 (477) [8]	Need for further interventions	Controlled cord traction plus immediate cord drainage *v* expectant management	4	0	0	0	0	High	
1 (200) [10]	Morbidity	Uterine massage *v* routine active management	4	0	0	0	0	High	
1 (200) [10]	Need for further interventions	Uterine massage *v* routine active management	4	0	0	0	0	High	
What are the effects of drug interventions to prevent primary postpartum haemorrhage?									
At least 7 RCTs (at least 3323 women) [11] [12]	Morbidity	Oxytocin *v* placebo/no intervention	4	−1	−1	0	0	Low	Quality point deducted for inclusion of quasi-randomised trials. Consistency point deducted for lack of consistent benefit
5 RCTs (at 2327 women) [11]	Need for further interventions	Oxytocin *v* placebo/no intervention	4	−2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for inclusion of quasi-randomised trial
At least 7 RCTs (at least 5030 women) [11] [13] [14]	Morbidity	Oxytocin *v* ergot compounds	4	−1	0	0	0	Moderate	Quality point deducted for inclusion of quasi-randomised trial
At least 4 RCTs (at least 3770 women) [11] [14]	Need for further interventions	Oxytocin *v* ergot compounds	4	−1	0	0	0	Moderate	Quality point deducted for inclusion of quasi-randomised trial
3 (445) [17] [18] [19]	Morbidity	Carboprost injection *v* ergot compounds	4	0	0	0	0	High	
2 (at least 529 women) [21] [20]	Morbidity	Carboprost injection *v* oxytocin plus ergometrine	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting
At least 3 RCTs (at least 3409 women) [22]	Morbidity	Ergot compounds *v* placebo/no intervention	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes		Morbidity, need for further interventions, mortality, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 RCTs (at least 2409 women) [22]	Need for further interventions	Ergot compounds *v* placebo/no intervention	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
At least 4 RCTs and 1 CCT (at least 2891 women) [11]	Morbidity	Oxytocin plus ergometrine combinations *v* ergot compounds	4	−1	0	0	0	Moderate	Quality point deducted for inclusion of controlled trial
At least 1 RCT and 1 CCT (at least 1927 women) [11]	Need for further interventions	Oxytocin plus ergometrine combinations *v* ergot compounds	4	−1	0	0	0	Moderate	Quality point deducted for inclusion of controlled trial
At least 5 RCTs and 1 CCT (at least 9332 women) [15]	Morbidity	Oxytocin plus ergometrine combinations *v* oxytocin alone	4	−1	0	0	0	Moderate	Quality point deducted for inclusion of controlled trial
At least 5 RCTs and 1 CCT (at least 9332 women) [15]	Need for further interventions	Oxytocin plus ergometrine combinations *v* oxytocin	4	−1	0	0	0	Moderate	Quality point deducted for inclusion of controlled trial
1 (46) [23]	Morbidity	Sulprostone injection *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (46) [23]	Need for further interventions	Sulprostone injection *v* placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (51) [23]	Morbidity	Sulprostone injection *v* oxytocin	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting
1 (661) [30]	Morbidity	Sublingual misoprostol *v* placebo/no intervention	4	0	0	0	0	Moderate	Quality point deducted for incomplete reporting
2 (150) [25] [26]	Morbidity	Sublingual misoprostol *v* oxytocin	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (100) [26]	Need for further interventions	Sublingual misoprostol *v* oxytocin	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
3 (370) [25] [26] [28]	Morbidity	Sublingual misoprostol *v* ergometrine	4	0	0	0	0	High	
2 (320) [26] [28]	Need for further interventions	Sublingual misoprostol *v* ergometrine	4	0	0	0	0	High	
1 (60) [29]	Morbidity	Sublingual misoprostol *v* oxytocin plus ergometrine combinations	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
At least 7 RCTs (at least 5153 women) [16]	Morbidity	Oral misoprostol *v* placebo/no intervention	4	0	−1	−1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for using ergometrine control as 'no intervention'
At least 7 RCTs (at least 1620 women) [16]	Need for further interventions	Oral misoprostol *v* placebo/no intervention	4	0	0	−1	0	Moderate	Directness point deducted for using ergometrine control as 'no intervention'
2 (2849) [16]	Mortality	Oral misoprostol *v* placebo/no intervention	4	0	0	0	0	High	
3 (at least 2423 women) [16]	Morbidity	Oral misoprostol *v* ergot compounds	4	0	0	0	0	High	
3 (at least 2223 women) [16]	Need for further interventions	Oral misoprostol *v* ergot compounds	4	0	0	0	0	High	
13 (at least 25145 women) [16]	Morbidity	Oral misoprostol *v* oxytocin	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results

Important outcomes		Morbidity, need for further interventions, mortality, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
11 (at least 24310 women) [16]	Need for further interventions	Oral misoprostol *v* oxytocin	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results
4 (20199) [16]	Mortality	Oral misoprostol *v* oxytocin	4	0	0	0	0	High	
4 (3805) [16]	Morbidity	Oral misoprostol *v* oxytocin/ ergometrine combinations	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results
4 (3805) [16]	Need for further interventions	Oral misoprostol *v* oxytocin plus ergometrine combinations	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results
1 (542) [16]	Morbidity	Rectal misoprostol *v* placebo/no intervention	4	0	0	0	0	High	
1 (546) [16]	Need for further interventions	Rectal misoprostol *v* placebo/no intervention	4	0	0	0	0	High	
3 (1780) [16]	Morbidity	Rectal misoprostol *v* oxytocin	4	0	0	0	0	High	
4 (2013) [16]	Need for further interventions	Rectal misoprostol *v* oxytocin	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results
2 (1262) [16]	Morbidity	Rectal misoprostol *v* oxytocin plus ergometrine combinations	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results
1 (798) [16]	Need for further interventions	Rectal misoprostol *v* oxytocin plus ergometrine combinations	4	0	0	0	+1	High	Effect-size point added for RR between 0.5 to 0.2
1 (120) [16]	Morbidity	Rectal misoprostol *v* carboprost injection	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
1 (120) [16]	Need for further interventions	Rectal misoprostol *v* carboprost injection	4	−1	0	0	+2	High	Quality point deducted for sparse data. Effect-size points added for RR greater than 5
1 (100) [33]	Morbidity	Vaginal misoprostol *v* placebo/no intervention	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between groups

Type of evidence: 4 = RCT; 2 = Observational
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio